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Biosimilar Medications – Savings Opportunities for Large Employers

A report for ERIC – The ERISA Industry Committee

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EXECUTIVE SUMMARY

The cost of biologic therapies is a key driver behind rising health plan costs. This study analyzed biologic spending by 13 large US employers to determine the savings opportunities for those large employers and their health plan beneficiaries if biosimilars were used instead of the reference biologics. The study also extrapolated savings to all employers that self-insure health coverage and the Medicare program.

Background

Biosimilars are therapies developed to compete with biologic products if the biologic patents and other market protections have expired. Biosimilars promote competition and add therapeutic options to the marketplace, helping reduce prices. This study aimed to identify the savings that large employers, members of ERIC (The ERISA Industry Committee), and their employees and families covered under the employer's health plan, could realize if the current demand for reference biologics was replaced by biosimilars. Over 150 million Americans have health insurance coverage through their employer, making up the largest proportion of the insured population.

Methods

Based on the market availability of biosimilars, the analysis focused on two drugs: filgrastim and infliximab. These were the first two drugs to have biosimilars introduced in the US market. ERIC member companies (plan sponsors) were invited to participate in this study. Companies that chose to participate were asked to provide data on utilization and spending on biologics and biosimilars from their prescription drug benefit and their medical health plans between January 01, 2018 and December 31, 2018. Potential savings due to plan adoption of biosimilars were calculated by comparing price differences between claims for the biosimilar and the reference biologic in our sample and applying these differences to current plan spending on reference biologics. Data on rebates were not available to the researchers.

Sample

A total of 28 pharmacy benefit managers and health plans providing service to 13 ERIC member companies provided data for this study. Participating companies reported an average of 2 million claims for prescription and medical drugs, spending an average of \$ 273.3 million dollars in 2018.

Findings

Spending on the two study drugs represented up to 2.7% of the typical company's annual spending on pharmaceuticals. Overall, biosimilars represented 68.8% of filgrastim claims but only 0.5% of infliximab claims, and there was marked variation in biosimilar utilization across different vendors for the same company. When matched for a series of characteristics to ensure an appropriate comparison, the biosimilar offered a median discount of 32% over the price of the reference biologic for infliximab and a median discount of 26% over the price of the reference biologic for filgrastim. Under these discount rates, the participating companies would have saved an average of \$1.53 million (range: 723 thousand – 4.93 million) on infliximab and an average of \$17,838 on filgrastim in 2018.

Biosimilar savings for beneficiaries in the 13 companies in terms of lower out-of-pocket costs were statistically significant due to a combination of lower frequency of coinsurance requirements and lower biosimilar list prices compared to beneficiaries taking the biologic. For infliximab, biosimilar users paid on average 12% less (about \$300) and filgrastim users paid on average 45% less (about \$600) out-of-pocket costs per year.

A comparison with price differentials obtained from external benchmarks - Average Sales Price and Wholesale Acquisition Cost - is presented. Across all the study and the external price metrics, biosimilar prices were lower than the biologic prices. Extrapolated to all employers who self-insure health coverage, potential savings at full biosimilar substitution could have amounted to \$407 million according to a market-based methodology and up to \$1.4 billion according to a company-size methodology in 2018. Potential savings to the Medicare program were estimated at \$279 million in 2018.

Conclusions

This study looked at the early diffusion of the first two drugs to have a biosimilar in the US market (filgrastim and infliximab). At full biosimilar substitution on these two drugs, the companies that participated in this study could have saved, on average, \$1.5 million in 2018. Biosimilar use also provided savings to the employees taking these drugs: out-of-pocket costs were significantly lower for beneficiaries taking the biosimilar when compared to beneficiaries taking the reference biologic. When extrapolated to all employers who self-insure health coverage, potential savings at full biosimilar substitution could have amounted to \$407 million to up to \$1.4 billion in 2018.

Rebates play a major role in biologic and biosimilar reimbursement, and the lack of information on company-specific rebates that might be paid to the pharmacy benefit manager/health plan and the self-insured company may have influenced our savings calculations. Confidential rebates are not available to the general public, but they should be made available to the plan sponsor.

For the biosimilars market to promote price competition and successfully generate savings, it is important that plan sponsors reconsider their options based on the full savings potential offered by each product. Increased transparency and greater access to information are an important first step.

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INTRODUCTION

Small Molecule Drugs – Branded Products

In order to be licensed for sale and marketing in the United States, a drug must be reviewed and approved by the US Food and Drug Administration (FDA). Conventional drugs are often called “small molecule drugs” because they tend to have small molecular size and non-complex chemical structure. When seeking FDA approval, branded “small molecule” drugs must provide evidence to ensure that the drug is safe and effective in its proposed use(s), that the drug’s benefits outweigh its risks, that the drug’s proposed labeling is appropriate, and that the drug’s manufacturing methods are adequate.¹

Small Molecule Drugs – Generics

A generic drug, as defined by the FDA,¹ is “a copy” of a conventional brand-name drug that has the same “active ingredient, conditions of use, dosage form, strength, route of administration, and (with certain permissible differences) labeling” but is produced by a different manufacturer.^a In order to be FDA-approved, a generic drug must provide evidence that its chemical composition is the same as the brand-name drug and that it is “bioequivalent,” meaning it “gets to the part of the body where the (branded) drug works at the same time and in the same amount”.¹ Because generic drugs have lower development and approval costs, they typically offer substantial discounts – at the magnitude of 80% or more - as compared with the price of the branded drugs, even though both have the same therapeutic effects.²

Biologics

Biologic therapies depend on biotechnology methods to be produced, which typically involves “living systems” to be produced – such as microorganisms (e.g., bacteria), plant cells, or animal cells – and tend to be more chemically complex than non-biologic drugs.³ Because of the complexity of biologic drugs’ production mechanisms and chemical structure, biosimilars have been regulated at much higher standards than generics [Exhibit 1]

Biosimilars

Biosimilars are therapies developed to compete with biologic products if the biologic market protections have expired. Like generic drugs, biosimilars promote competition and add therapeutic options to the marketplace, helping reduce prices and offering an opportunity to bring down drug spending. Biosimilars are subject to stricter regulations and there are more barriers to the uptake of biosimilars in the US market than generic drugs, such as no automatic interchangeability.

^a However, according to the FDA, a generic drug “may have certain minor differences from the brand-name product, such as different inactive ingredients.”

The pathway for FDA approval of biosimilars in the US was created by the Biologics Price Competition and Innovation Act (or BPCIA) as part of the Affordable Care Act (ACA), enacted in 2010. Different than generic drugs, that are considered to be bioequivalent to the reference branded products, biosimilars are defined as “highly similar” to, and having “no clinically meaningful differences in safety, purity, and potency” from an existing FDA-approved reference biological product.⁴ Biologic drugs depend on “living systems” such as microorganisms (e.g., bacteria) or cells, and tend to be more chemically complex than non-biologic drugs.³ Because of the complexity of biologic drugs’ production mechanisms and chemical structure, biosimilars have been regulated at much higher standards than generics [Exhibit 1].

Similarities and Differences between Biosimilars and Generic Drugs

For the approval of a non-biologic, “small molecule” generic, the FDA requires bioequivalence studies demonstrating that the generic has the same chemical composition, purity and quality as the reference product, as well as the same bioavailability in healthy volunteers.⁵ Once approved for marketing, a generic becomes substitutable for the branded reference product at the pharmacy without the need for a new medical prescription.

In contrast, for the approval of a biosimilar, the FDA requires a series of studies, such as analytical (in-vitro) studies demonstrating “highly similar” chemical composition to the reference product, purity and quality; toxicity studies on animal models; and comparative clinical studies on patients with the clinical condition, demonstrating that the safety and effectiveness of the biosimilar product, its immunogenicity, and its pharmacokinetics and pharmacodynamics are expected to be the same as the reference biologic.⁶

Differently than generic drugs, biosimilars do not become directly substitutable for the reference product upon approval. While a patient holding a prescription for a branded product may be dispensed the generic, a patient who is prescribed the reference biologic needs a new prescription from their medical provider if they would like to get the biosimilar instead.^b The direct substitutability for the reference product is only granted to a biosimilar product if the manufacturer of the biosimilar carries out a specific type of clinical trial – often called a “switching study”- where patients with the clinical condition treated by the drug are exposed to the reference product, the biosimilar, and again the reference product in a sequence, and monitored for clinical effectiveness and safety.

In addition to the lack of substitutability for the reference products, there are many other barriers to the use of biosimilars in the US market. Different than conventional branded and generic drugs, biosimilars and biologics do not share the same non-proprietary name (proper name, or “generic” name).^{7, c} This difference contributes to generating confusion among prescribers, pharmacists, and patients.⁸ Disinformation and uncertainty about biosimilars is often reflected in patients and providers’ reluctance to switch products.⁹ Lastly, price negotiations that rely heavily on drug rebates and discounts may favor the utilization of the biologic over the biosimilar.¹⁰

^b Pharmacists often perform this function via a call to the physician, so the patient may not necessarily need to take action in order to obtain the new prescription.

^c Until March 2020 all biosimilars had a random 4-letter suffix added to their non-proprietary names. After March 2020 all biologics, including reference products and biosimilars, will have different, random 4-letter suffixes added to their non-proprietary names.

Biosimilars Today

There are 26 biosimilars approved for sale in the US market today [Exhibit 2].¹¹ Despite so many approved products, only a few biosimilars are actually available in the market. Many approved biosimilars have not been launched because of patent disputes and other legal challenges between the manufacturer of the reference product and the manufacturer of the biosimilar. To date, only two drugs have had more than one biosimilar launch in the US market: filgrastim and infliximab. These drugs have seen their first biosimilars offer about 15% list price reductions over the reference biologic.¹² However, as is common in the pharmaceutical industry, the list price may have little relation to the actual transaction price. The market entry of the second biosimilar has been associated with more substantial price decreases. [Exhibit 3].

In spite of the multiple barriers, the Congressional Budget Office (CBO) has estimated that the use of biosimilars could generate savings of about \$25 billion over 10 years, roughly 0.5 percent of national spending on prescription drugs.¹³ Some of the assumptions regarding the biosimilars market come from the European experience. The European Medicines Agency established a pathway for the regulation of biosimilar drugs six years before the FDA. There are over 70 biosimilar drugs currently available in the European market with widespread utilization, generating millions in savings.¹⁴ The RAND corporation estimated that biosimilars could reduce spending in the US market by \$54 billion from 2017-2026.¹⁵ Several other studies have followed, demonstrating a potential for cost savings from biosimilars to both patients and plan sponsors in the US.¹⁶⁻¹⁹ Because biologics represent a large source of drug expenditures in the US today, biosimilars represent a significant opportunity to reduce costs. However, it is unclear what are the actual savings from biosimilars in practice in the US.

Opportunities for Employers that Self-Insure Health Coverage

About half of Americans who have health insurance today receive their coverage through their employer.²⁰ Large employers generally do not purchase health insurance for their employees, but rather offer health coverage through a self-insured health plan.²¹ Of US employers offering health insurance, the majority (61%) offers health coverage through a self-insured health plan.²¹ All ERIC member companies sponsor self-insured health plans for their employees. Some also purchase health insurance in certain circumstances, such as for small populations of employees in a geographic area. The cost of biologics is equally challenging in the case of purchased health insurance but not addressed in this study.

Employers that self-insure their health coverage bear the risk of losses in their health insurance pool. Therefore, significant increases in their pharmaceutical cost raise the need for an offset elsewhere, often resulting in increased premiums or cost-sharing for employees. Responsible management including measures to control drug costs is important in order to preserve employees' benefits while preventing premium and cost-sharing increases. This is especially important to workers enrolled in high-deductible health plans (HDHPs), who bear the burden of high drug prices even more directly.

Most employers with self-insured health plans contract with a pharmacy benefit manager (PBM) to manage their prescription drug benefit, i.e. manage the coverage of drugs used in an outpatient setting. Most self-insured employers also contract with at least one medical health plan vendor to manage their medical benefit, i.e., the coverage of medical services. The medical benefit includes doctor visits, hospitalizations, and procedures, including drugs administered in a medical setting - for example, drugs that require an intravenous infusion in a physician practice or in a hospital outpatient department. It is common for a self-insured employer to contract with multiple health insurance carriers in order to offer a choice of multiple health insurance plans for their employees.^d

In both the prescription and the medical benefit, drug coverage is typically determined by a drug formulary. Usually, the PBM sets the drug formulary for the prescription benefit, determining the drugs to be covered for outpatient use and the medical health plan vendor sets the drug formulary for the medical benefit determining the drugs that will be covered in the medical setting. While designing the formulary, the PBM or the medical carrier simultaneously negotiates the prices of the drugs that will be covered. Usually, the pharmaceutical manufacturers will provide price concessions (discounts and rebates) for the opportunity of placing their drug in the formulary.²²

The drug formulary lists the drugs that will be covered and specifies the requirements that are in place in order to access the drug. For example, whether a drug requires the doctor to submit clinical information in order to obtain a special authorization from the plan (“prior authorization”). In addition, the drug formulary specifies how much cost-share the beneficiary is required to pay in order to access the drug. There are two main types of cost-share: a “copayment,” in which the patient is required to pay a fixed-dollar amount for each prescription, or a “coinsurance,” in which the patient is required to pay a percentage of the drug cost of each prescription.

When patients are required to pay a coinsurance, the amount is calculated over the list price of the drug. This means that, even if the PBM or the medical plan vendor was able to negotiate a lower drug price for the plan sponsor, the beneficiary may not benefit from that price negotiation. The drug’s list price is typically the highest price of a drug, and because of price negotiations, no plan sponsor ever actually pays the list price. However, beneficiaries may face the drug’s full list price when they are required to pay a coinsurance, when the level is often based on the list price, or when they are in the deductible phase, when they are required to pay the list price in full for their drugs. This is a problem especially for beneficiaries enrolled in HDHPs, where they are required to pay full list price until their high deductible is met. As of 2018, this represented 29% of workers with private health insurance.²¹

Study Aims

The goal of this study was to assess the savings that large employers, members of ERIC (The ERISA Industry Committee), and their employees and families covered under the employers’ plans, could obtain if the current usage of the reference biologics was replaced by biosimilars. First, we sought to identify the extent to which the company’s beneficiaries were being treated with reference biologics or

^d In certain cases, the medical health plan vendor may also manage the outpatient prescription drug benefit, in which case the self-insured employer will not directly contract with a PBM (“carve-in” model).

with biosimilars in practice. Next, we estimated the potential savings that could be obtained if the beneficiaries that were treated with a reference biologic had been treated with a biosimilar instead.

METHODS

Data Sources

ERIC member companies (plan sponsors) were invited to participate in this study. Companies that chose to participate were asked to provide data on utilization and spending on biologics and biosimilar drugs from their prescription drug benefit and their medical health plan benefit. Because each self-insured plan sponsor could contract with multiple vendors (PBMs and/or medical insurance carriers) to manage their health insurance plans and drug benefit (“data donors”), each participating company could provide more than one source of data.

Time Frame

All information reflected the plan sponsors’ spending and utilization between January 1, 2018 and December 31, 2018.

Study Drugs

Based on the market availability of biosimilars, the analysis focused on two drugs: filgrastim and infliximab. These were the first two drugs to have biosimilars introduced in the US market. Because each of these drugs had two biosimilars available in the market at the onset of this study, the analysis included a total of six different products [Exhibit 4]. It is important to mention that the savings are likely to be greater when there are two or more biosimilars on the market.²³

For infliximab, the analysis included the reference biologic Remicade® and the biosimilars Inflectra® and Renflexis®. The reference biologic was launched in the US market in 1998 and has eight FDA-approved indications. The biosimilars were launched in the US market in 2016 and 2017 respectively and are FDA-approved for the same indications as the reference product. Infliximab is mainly used as an immunosuppressant to treat patients with auto-immune conditions, such as rheumatoid arthritis, Crohn’s disease, ulcerative colitis, and others.

For filgrastim, the analysis included the reference biologic Neupogen®, the biosimilar Zarxio®, and the alternative biologic Granix®. The reference biologic was launched in the US market in 1991, and the biosimilar was launched in 2015. A second biosimilar (Nivestym®) was launched in 2018, but there was no utilization for these products recorded by the participating companies, and therefore it was not part of the study. The alternative biologic was approved before the biosimilars pathway was fully implemented, and therefore it was never designated as a biosimilar. Filgrastim is an adjunctive treatment for patients undergoing chemotherapy. Filgrastim works by stimulating the production of

blood cells, and therefore, is also used in other conditions where blood cell counts are too low. The reference product has six FDA-approved indications, and the biosimilar is approved to treat five of them (the indication that is not approved for the biosimilar is a very rare condition where patients have symptoms after being exposed to acute radiation). The alternative biologic is only approved to treat one of the six reference product indications. Yet, it is widely used in clinical practice as a competitor to the reference product,²⁴ and therefore in this study we treated it as a biosimilar.

Data Collection

Data collection was performed using a standardized data collection template that aggregated information at the drug level. The goal was to perform an apples-to-apples comparison. For each drug, the following information was collected: total number of users, total number of claims, total spend, average age of the users, percentage of users who were female, type and level of cost-share required from the beneficiaries to access the drug, average out-of-pocket costs to beneficiaries, and the clinical conditions for which each drug was prescribed. Because the data was collected in aggregated form per drug, no patient information was collected. In addition to the drug-specific information, participating companies were requested to report their overall number of beneficiaries and pharmaceutical benefit spend.

Data Analysis

The data analysis was implemented through a series of descriptive statistics, regression models, and graphics using Stata statistical package version 15 (StataCorp, College Station, TX). Most descriptive statistics were aggregated at the level of company (plan sponsor) or vendor (data donor). When applicable, data was weighted by number of claims or number of users of each product.

Savings Calculations

Potential savings due to plan adoption of biosimilars were calculated by comparing price differences between the biosimilar and the reference biologic and applying these differences to current plan spending on reference biologics. We estimated savings to plan sponsors under two scenarios: 100% adoption of biosimilars (if all beneficiaries who took the reference biologic in 2018 had taken a biosimilar instead), and 50% adoption of biosimilars (if half of the beneficiaries who took the reference biologic in 2018 had taken the biosimilar instead).

The price comparison between biologic and biosimilar was implemented by comparing the negotiated prices for each drug from the claims data in our sample. The goal was to allow for an apples-to-apples comparison. The comparison matched the price per claim paid for the biosimilar and biologic with the same active ingredient, dosage form and strength, within the same plan sponsor (ERIC member company) and data donor (medical or prescription benefit vendor). The matching technique was needed because negotiated prices for drugs vary according to the drug's market share, and there was a very large variation in market share for biologics and biosimilars between data donors from the same company and across participating companies. In addition, the price comparisons included only drugs

where claims for the biologic and biosimilar contained a similar number of units and where the vendor had reimbursed at least one claim for the reference biologic and all corresponding biosimilars over the course of the year. This strict comparison approach was intended to capture prices that could actually be compared. Namely, the strategy aimed to exclude vendors where the reference product placed a “rebate wall”, i.e., where the payor was contractually required to purchase exclusively the biologic in exchange for deep price concessions.¹⁰ Contractual terms and price concessions are not observable, which may have limited the inferences from our analysis. Rebates play a major role in biologic and biosimilar reimbursement, and due to the lack of information on company-specific rebates that might be paid to the PBM/medical vendor and the self-insured company, our potential savings estimates should be viewed as minimum levels of rebates to achieve cost parity between biosimilars and biologics.

Lastly, the out-of-pocket differences observed between employees taking the biosimilar and the biologic in our sample were also used to estimate how much employees would have saved if the beneficiaries who took the biologic had switched to the biosimilar instead.

Sensitivity Analysis: Accounting for Drug Rebates

The negotiated prices of drugs in our sample reflect negotiated discounts but do not account for rebates provided by drug manufacturers. Drug rebates are typically realized months after each claim is finalized and are not necessarily traceable back to each claim. For example, drug rebates may be negotiated as a “bundle” and depend on the market share of other drugs in the manufacturer’s portfolio, not only the drugs of interest in this study. Rebates are negotiated at the contractual level with each benefit vendor and plan sponsor and are, therefore, confidential information. Companies in the study may know this information for their company.

To assess the robustness of our results, a sensitivity analysis was implemented in two steps. First, we compared the price differentials obtained by our original matching criteria (strict criteria) to the price differential obtained across all biologic and biosimilar pairs within the same company (plan sponsor) and benefit vendor, as long as the drugs were matched by active ingredient, dosage form, and strength.

Next, we compared the study results to two external price benchmarks: Wholesale Acquisition Cost (WAC), a measure of drug prices that does not account for any discounts or rebates²⁵ and Average Sales Price (ASP), a calculated price defined in regulation by the Medicare program that reflects the “weighted average of all manufacturer sales prices” and includes all rebates and discounts that are privately negotiated between medical and prescription benefit vendors and drug manufacturers.^e The ASP methodology is presumed to mirror the reimbursement for physician-administered drugs in the commercial market and it is calculated by CMS.²⁶ All price comparisons were implemented for biosimilar and reference biologic drugs matched by the same active ingredient, dosage form, and strength.

Extrapolating Savings

An extrapolation of savings to other employers that self-insure health coverage was implemented in two ways. First, the savings were extrapolated by multiplying the savings found in our sample of 13

^e Medicaid and certain federal discounts and rebates are exempted from the ASP calculation.

companies by the inverse of the proportional ratio of the self-sponsored employer health insurance market represented by the participating companies. Second, we used publicly available 2018 sales data for each of the biologics under study (Remicade® and Neupogen®).^{27,28} We assumed that employers represented 50% of the market for these drugs, and that self-insured employers represented 61% of the employer-sponsored health insurance market. We then applied the biosimilar discount ratios found in this study to the estimated self-insured employers' spending on each of the biologics.

An extrapolation of savings to the Medicare program was implemented by applying the discount ratio between the biosimilar and the biologic using ASP prices to Medicare's total spending on the biologic in 2018. Because the Medicare Part B program accounts for over 95% of infliximab utilization and over 80% of filgrastim utilization, the Medicare savings were calculated for the Part B program only. ASP prices were obtained from the July 2018 CMS Payment limit²⁹ and Medicare utilization and spending rates were obtained from the 2018 CMS Medicare Drug Spending Dashboard & Data.³⁰

Confidentiality and Data Protection

The identity of the participating companies and their vendors was kept confidential. When required, non-disclosure agreements were established for data transfer. The study was exempt from review by internal review boards because it did not constitute human subjects research.

RESULTS

Overview of data sources and participating companies

A total of 13 companies participated in this study, representing a diverse set of industries, ranging from the food and beverage to the technology industry [Exhibit 5]. Most companies were in the technology sector, followed by the financial sector.

Reflecting the multiple different benefit packages provided by the participating companies, a total of 28 different data sources were included in the study ("data donors"). Some were health insurance plans providing medical benefits while others were PBMs providing prescription drug benefits. All companies that participated provided PBM data. Out of the thirteen companies that participated, two companies provided PBM data only; seven companies provided data from their PBM plus one medical health insurance vendor; and four companies provided data from their PBM plus two medical health insurance vendors.

Data donors (i.e., the different vendors of prescription and medical benefits who provided data for this study) included the three largest PBMs (which together comprehend more than 80% of the US prescription drug benefit market),²³ as well as a variety of major medical insurance carriers.

Participating companies reported an average of 174.8 thousand beneficiaries in 2018 (minimum of 21 thousand and maximum of 484 thousand beneficiaries). These companies reported an average of 2 million claims for prescription and medical drugs, spending an average of \$273.3 million dollars (minimum \$290 million and maximum \$569 million) in 2018 [Exhibit 6].

Study Drugs: Utilization and Spending Overview

These are expensive drugs, but these drugs are not used by many patients in the employed population. The study drugs (infliximab and filgrastim) were used by an average of 186 users in each company in 2018 (minimum 18 and maximum 683 users). These drugs generated an average of 1,176 claims and average spending of \$4.7 million (range: \$288 thousand to \$16.6 million) [Exhibit 7].

Patients using the study drugs varied in age between 9.7 years and 74 years old. On average, a patient using the study drugs was 48.7 years old. About 55% of users were women (minimum 26% - maximum 81%). Although the users represented a small minority of the overall beneficiaries in these companies (on average, only 0.06%), the spending on these two drugs represented up to 2.7% of the typical company's total spending on pharmaceuticals during the year 2018.

Most of the utilization and most of the spending occurred through the medical benefit – on average, 83% of all claims and 86% of the spending was channeled through the medical health plan vendors, and only 17% of claims and 14% of spending through the prescription benefit vendors. This is because the drugs are typically physician administered drugs and are paid under the medical benefit.

Comparison: Infliximab vs. Filgrastim

Infliximab had greater utilization and spending than filgrastim. Overall, companies spent an average of \$4.8 million on infliximab in 2018 (range: \$226,417 to \$15.6 million) and an average of \$254,486 on filgrastim (range: \$8,776 to \$983,607) [Exhibit 8a].

Infliximab was used by more beneficiaries and cost more per claim than filgrastim. On average, infliximab was used by 172 beneficiaries per company (range: 10 - 534 beneficiaries), while filgrastim was used by 59 beneficiaries per company (range: 1 - 198 beneficiaries). Each claim for infliximab costed the plan sponsor an average of \$4,762, while each claim for filgrastim cost, on average \$903. In total, each beneficiary using infliximab cost the plan sponsor an average of \$28,111.83, while each beneficiary using filgrastim cost the plan sponsor an average of \$4,550.65 [Exhibit 8b-d].

Comparison between Biologics and Biosimilars: Overall Utilization and Spending

The utilization of biosimilars varied considerably by drug. Overall, 68.8% of filgrastim claims went to buy the biosimilar^f but only 0.5% of infliximab claims went to buy the biosimilar [Exhibit 9].

For the same drug, the share of biosimilar utilization varied across the different data donors [Exhibit 10a-b]. Most of the vendors for infliximab had less than 1% of utilization for the biosimilar (16 out of 26 data donors had 0% biosimilar utilization), but for one vendor the biosimilar represented a total of 5.15% of infliximab claims. Although for filgrastim the biosimilar had much greater utilization, there were still three vendors for which the biosimilar represented 0% of all filgrastim claims. All other

^f We treated the alternative biologic tbo-filgrastim (Granix®) as a biosimilar for the purposes of this analysis. A sensitivity analysis excluding this drug did not significantly change the results.

vendors for filgrastim had at least 30% of claims for the biosimilar, with 3 vendors reporting 100% of the filgrastim claims for the biosimilar.

Because plan sponsors contracted with multiple vendors, there was significant variation in the percentage utilization of biosimilars across different vendors for the same plan sponsor [Exhibit 11a-c] For the same drug and same company, the differences between vendors could be as striking as having one vendor at 0% biosimilar utilization and the other vendor at 100% biosimilar utilization, which occurred in the case of filgrastim. This is important because utilization determines the price concessions that manufacturers will provide on their drugs. Therefore, such striking differences in utilization mean that vendors may be offering strikingly different prices on the same drugs for their plan sponsors.

Comparison between Biologics and Biosimilars: Patient Characteristics

Overall, patients using the biosimilar tended to be older than patients using the biologic for both study drugs [Exhibit 12a-b]. A greater percentage of women tended to take the biosimilar rather than the biologic infliximab, but a lower percentage of women tended to take the biosimilar rather than the biologic filgrastim. While these differences are statistically significant, their meaning is unclear. It is likely that, to some extent, these differences reflect the conditions that the different products were being used to treat.

When analyzing the conditions that the drugs were prescribed for, we found that the biologic and the biosimilar were similarly likely to have been prescribed to treat an off-label condition (about 10% for all drugs) [Exhibit 13a-b]. The exception was the alternative biologic tbo-filgrastim (Granix®), which was used to treat an off-label condition in over 50% of cases. This suggests that the alternative biologic Granix® may be prescribed for more indications than the one indication that it is approved to treat, likely behaving in clinical practice as a competitor for the reference biologic in more cases than its one approved indication would indicate.

It is also possible that the differences in patient characteristics may reflect different uptake patterns by prescribers treating certain conditions, or different acceptability patterns of patients who have certain conditions. Rheumatoid arthritis for example, one of the main indications of infliximab, is a condition that predominates among women. If rheumatologists were more amenable to prescribing the biosimilar, or if rheumatoid arthritis patients were more likely to accept the biosimilar, this pattern would be consistent with the results that we obtained. Our data, however, does not allow us to investigate such relationships. We are also not able to examine whether the venue where patients are treated might have influenced the product utilization.

Most likely it is payment and billing practices that differ across hospitals and physician practices, favoring one or the other product. Rebates to physicians and hospitals may be greater for the biologic or biosimilar depending on the negotiation. Or, a certain type of facility may be under different contractual terms with the benefit vendor allowing it to charge more or less for the biologic or the biosimilar. If one patient population were treated more frequently in a certain type of venue, this could also influence the demographic differences that we observed.

How are Patients Paying for their Biologics and Biosimilars? A comparison of out-of-pocket spending

Overall, the majority of patients are required to pay a coinsurance in order to obtain both of the drugs in our study. Patients utilizing biosimilars tended to be required coinsurance less frequently than patients utilizing the reference biologic for both drugs, infliximab (76.7% for biosimilar vs. 85.4% for biologic on average) and filgrastim (90.8% for biosimilar vs. 95.2% for biologic, on average), but this difference was only statistically significant in the case of filgrastim [Exhibit 14a-b]. When required a coinsurance, the percentage of the cost of the drug did not vary between biologics and biosimilars, being on average about 20% for infliximab products and 22% for filgrastim products.

Overall, patients taking the biosimilar had lower out-of-pocket payments than patients taking the biologic, over the course of the year 2018. Infliximab biologic users paid on average \$2,890.27 in out-of-pocket costs and biosimilar users paid on average \$2,533.20 over the course of the year ($p=0.056$). This means that biosimilar users paid about \$330 less out-of-pocket than biologic users over the course of the year, on average, a difference of about 12%.

Filgrastim biologic users paid an average \$1,319.87 out-of-pocket, while biosimilar users paid on average \$721.01 over the course of the year 2018, a difference that was statistically significant ($p<0.0001$). This means that biosimilar users paid almost half out-of-pocket cost than biologic users, a difference of about \$600.

A combination of lower frequency of coinsurance requirements and lower biosimilar list prices is likely to have explained the differences that we found. While most plan sponsors tend to have out-of-pocket maximums in place, the information on out-of-pocket costs collected in this study reflects true payments incurred by the beneficiaries and therefore suggests that these expenditures were lower than the maximum.

It is important to mention that our data does not contain information on whether the patients received coupons or used patient assistance programs to help pay for their drugs. Coupons and patient assistance programs are designed to help patients afford prescription drugs by reducing their out-of-pocket costs.³¹ If patient assistance programs or coupons were available to some, but not all products or patients examined in our study, they might have differentially influenced our findings.

Price Comparison between Biologics and Biosimilars

The price comparison was implemented comparing the median price differential across drugs within the same data donor and plan sponsor, matching biosimilar and reference biologics with the same active ingredient, dosage form and strength, where the claims for the biosimilar and the reference biologic had a similar number of units and where the data donor had at least one claim for the biologic and for the corresponding biosimilars during the year 2018. This matched price comparison included a total of two drug pairs for infliximab and seven drug pairs for filgrastim. **The comparison found that, when matched for all characteristics, the biosimilar price represented 68% of the price of the biologic for infliximab and 74% of the price of the biologic for filgrastim. [Exhibit 15].** This means that the biosimilar offered a

median discount of 32% over the price of the reference biologic for infliximab and a median discount of 26% over the price of the reference biologic for filgrastim.

Savings calculations: How much could plan sponsors save by increasing biosimilar utilization?

Under the estimated discounted rates described above, the participating companies would have saved an average of \$1.53 million (range: 723 thousand – 4.93 million) on infliximab and an average of \$17,838.01 (range: \$2,281.76 – \$ 87,801.74) on filgrastim during the year 2018 [Exhibit 16 a-b].

Company-specific savings depended mostly on two dimensions: the number of beneficiaries utilizing each drug, and the percentage of biosimilar use currently achieved by the company. Companies with low drug utilization had the lowest savings and companies with large utilization and low biosimilar market share had the highest estimated savings [Exhibit 17a-b].

Sensitivity Analysis

Relaxing the matching criteria that we utilized to estimate the price differentials in our study, we compared the median price differential across all drug pairs from the same data donor and plan sponsor, as long as the biosimilar and the reference biologic had the same active ingredient, dosage form and strength. This approach yielded a total of eight drug pairs for infliximab and 29 drug pairs for filgrastim. **In this approach, the biosimilar price represented 75% of the price of the biologic for infliximab and 84% of the price of the biologic for filgrastim. [Exhibit 18 a-b].** This means that the biosimilar offered a median discount of 25% over the price of the reference biologic for infliximab and a median discount of 16% over the price of the reference biologic for filgrastim.

The comparison with external price benchmarks found that, for infliximab, the biosimilar price was, on average, 23% lower than the biologic according to the ASP, and 19% lower than the biologic according to the WAC. For filgrastim, the biosimilar price was, on average, 36% lower than the biologic according to the ASP, and 17% lower than the biologic according to the WAC [Exhibit 19 a-b].

Across all internal and external metrics, biosimilar prices were lower than the biologic prices. Although our study results did not account for rebates, they have the same direction suggested by the ASP calculation. Given the wide variation in utilization and market share of products that we identified in our sample, it is likely that companies may be obtaining a wide range of price differentials. The level of rebates may not be disclosed to the general public, but they should be made available to the plan sponsor.

Savings Extrapolation to All Employers that Self-Insure Health Coverage

The 13 companies that participated in this study represented 1.5% of the US employer-sponsored health insurance market.^{21,22} Assuming that all employers that self-insure health coverage had the same utilization pattern than the companies that participated in this study, and that all employers that self-insure health coverage were to achieve 100% biosimilar substitution, the savings to all on the two study drugs obtained through our first extrapolation approach would amount to a total of \$1.4 billion in 2018.

It is important to note that this study found a large variation in the savings per each participating company; therefore, this estimate may not accurately reflect the potential savings.

Through our second, market-based savings extrapolation approach, we estimated the US employer-sponsored insurance market to be approximately half of the US market of Remicade® and Neupogen®. We then estimated that self-insured employers represented 61% of the US employer-sponsored insurance market. Applying the biosimilar discount rates found in our study to the estimated market size of these two drugs, the potential savings to all employers that self-insure health coverage would amount to a total of \$407 million in 2018.

Savings Extrapolation to the Medicare Program

In 2018, the Medicare Part B program had 65.2% biosimilar utilization for filgrastim and 10.7% biosimilar utilization for infliximab. At 100% biosimilar utilization, and assuming discount rates of 23% for infliximab and 36% for filgrastim as estimated based on ASP prices, the Medicare Part B program could have saved a total of \$279 million in 2018 (\$264.4 million on infliximab and \$14.5 million on filgrastim).

DISCUSSION

This analysis included 13 of America's largest employers offering self-insured health coverage to their nationwide workforce and the many prescription drug and medical health insurance plan vendors with whom these companies contract in order to manage the benefits that they offer to their employees and families.

The study examined two specific drugs – filgrastim and infliximab – that were the first drugs to have biosimilars in the US market. We found that these drugs were used by a very small percentage of the companies' beneficiaries but accounted for up to 3% of the companies' overall drug spending. One drug in particular – infliximab – had the most utilization and spending. This drug is also where the lowest biosimilar utilization occurred – in most companies, less than 1% of all infliximab claims were dispensed with a biosimilar product - and therefore presented the largest opportunity for savings.

The savings to plan sponsors were estimated at an average of \$1.53 million dollars per year (range: \$723 thousand to \$4.93 million) on infliximab alone, if all the current biologic utilization had been replaced by the biosimilar. At 50% substitution rate, plan sponsors could save close to a million dollars a year on this one single drug. Savings on the second study drug (filgrastim) were much more modest, due to much lower utilization, lower price, and higher current biosimilar market share (average of 68% of biosimilar utilization across all participating companies).

When the biosimilar discount rates estimated in this study were extrapolated to all employers that self-insure health coverage, the potential savings amounted to \$407 million according to a market-based methodology, and up to \$1.4 billion according to a company-size methodology. The Medicare Part B program had greater biosimilar utilization in 2018 and different estimated discount rates based on ASP prices; when extrapolated to the Medicare Part B program, savings from full biosimilar substitution for the two drugs in this study would have amounted to a total of \$279 million in 2018.

While the price comparisons and savings estimates reflected prices negotiated on behalf of plan sponsors by their prescription drug benefit managers and medical health insurance plan vendors, these analyses did not account for confidential drug rebates that are passed on to the plan sponsor according to the market share and formulary placement of each drug. Yet, our estimates provide an assessment of the minimum levels of rebates that should be offered by reference biologic manufacturers to achieve cost parity between biosimilars and biologics.

In addition, the comparisons between our estimates and other price benchmarks – drug list prices before rebates and discounts, and CMS-calculated average sales prices that account for both rebates and discounts – suggest that our estimates may reflect true price relationships and realistic potential savings under the different substitution rates scenarios.

Of note, none of the discounts or rebates that get negotiated on behalf of plan sponsors are available to beneficiaries. Up to 95% of beneficiaries taking the study drugs were requested to pay a percentage of the drug's price in order to obtain the drugs they needed. Our analysis showed that beneficiaries taking the biosimilar have statistically significantly lower out-of-pocket spending than beneficiaries taking the reference biologic. Because out-of-pocket payments are calculated over the drug's list price, before rebates and discounts, our findings suggest that beneficiaries will be better-off by utilizing a biosimilar. In the case of filgrastim, the out-of-pocket spending of beneficiaries taking the biosimilar was, on average, 45% lower than the out-of-pocket spending of beneficiaries taking the biologic.

Although our study did not obtain patient-specific information, the aggregated characteristics of the beneficiaries taking each product suggested that beneficiaries taking the biosimilar tend to be older than those taking the biologic, in both study drugs. Biosimilar utilizers tended to be more frequently female in the case of infliximab and more frequently male in the case of filgrastim as compared to the biologic utilizers. Although these differences are statistically significant, their meaning could not be further explored given the nature of the data collected in this study. It is likely that these characteristics may reflect health conditions, patient preferences, physician prescribing practices, or the characteristics of the locations where patients receive care and may be more conducive to the use of one over the other product. It is important that such factors be explored by further studies focusing on patient and provider behavior, and on facility purchasing and reimbursement practices.

There was no significant difference in terms of off-label utilization between biologics and biosimilars except for the biologic alternative Granix[®] (tbo-filgrastim). This drug is approved for only one out of the reference biologic's six indications, and yet it seems to behave as a competitor to the reference biologic in more clinical situations than the FDA-label would allow. Different than the other products, whose off-label use represented about 10% of cases, Granix[®] was used for an off-label indication in more than half of patients. This behavior is one of the reasons why Granix[®] was treated in our study as a biosimilar when implementing the statistical analyses.

Drug price negotiations in the US depend heavily on drug rebates and discounts that are negotiated confidentially between the plan sponsor (represented by the PBM or insurance carrier) and drug manufacturers.³² Information on rebates and discounts is not public, therefore it is possible that the true difference in price between the reference biologic and their biosimilar(s) may be higher or lower than the estimates found in our study. Confidential rebates are defined in contractual provisions between each plan vendor (PBM or health insurance carrier) and drug manufacturers. These contractual

arrangements are not available to the general public, but they should be made available to the plan sponsor.

Coupons and patient assistance programs are also available to patients with employer-sponsored health insurance. These programs are designed to help patients afford prescription drugs by reducing their out-of-pocket costs. However, these programs are more likely to cover expensive specialty drugs and branded drugs than the corresponding generics or less expensive therapeutic alternatives.³¹ It is possible that the availability of coupons or patient assistance programs also may influence patients' or providers' choice of product, for example, if these programs were more likely to cover the biologic over the biosimilar. This question, however, is beyond the scope of our study.

Our study found that there was a large discrepancy of biosimilar market share between different vendors for the same company. This means that the likelihood of a beneficiary receiving a "better deal" in their drug benefit does not depend on the company that they work for, but rather, on their choice of health plan or drug benefit carrier. In addition, a large variation in biosimilar market share for the same company is inefficient. Most drug savings depend on the size of the market share. Companies whose market share is fragmented across multiple products may not be benefitting from all the savings that they could, as our empirical price comparisons have showed. However, they may benefit from the volume of their PBM or medical plan vendor.

The striking differences in number of users, drug prices, plan spending and biosimilar market share across the two drugs in our study (filgrastim and infliximab) are reflective of the multiple factors that determine drug utilization and biosimilar market penetration. While there are important clinical differences between these two drugs – filgrastim being for used in recurrent occasions and having clear biomarkers to monitor its effect, for example, while infliximab is a drug for chronic use without good biomarkers to monitor its benefits – it is likely that non-clinical factors also play an important role in determining biosimilar uptake. For example, payment systems that rely on high rebates may favor the more expensive biologic rather than the cheaper biosimilars.³³ At their extreme, such reimbursement incentives may generate "rebate traps" where the plan sponsor will be better-off by purchasing the reference biologic exclusively,¹⁰ a choice that penalizes beneficiaries with higher out-of-pocket costs as our study has shown.

It is also possible that the difference between the two drugs reflects different levels of maturity in the biosimilars market. While filgrastim was the first drug to have a biosimilar introduced in the US market and has had two biosimilar competitors in the market for the last five years, infliximab biosimilars had been available for little over a year at the beginning of our study period. It is possible that, as the infliximab market matures, the market uptake of the biosimilar may increase.

The entry of competitors in markets where the reference products have lost patent protection is intended to bring costs down and offer greater therapeutic choices. For the biosimilars market to promote price competition and successfully generate savings, it is important that plan sponsors reconsider their options based on the full savings potential offered by each product. Having access to this information requires that plan sponsors be allowed to know and be able to audit all the contractual arrangements between their PBM and health insurance benefit vendors and drug manufacturers. Plan sponsors may increase the efficiency of their price negotiations and achieve substantial savings for their organizations as well as their beneficiaries. Increased transparency and greater access to information are important first steps.

CONCLUSIONS

This study looked at the early diffusion of the first two drugs to have a biosimilar in the US market (filgrastim and infliximab). The bottom line is that when matched for all characteristics, the biosimilar price represented 68% of the price of the biologic for infliximab and 74% of the price of the biologic for filgrastim, and patients who took the biosimilar paid on average 12% and 45% less out-of-pocket than those who took the biologic, respectively.

At full biosimilar substitution on these two drugs, the companies that participated in this study could have saved, on average, \$1.5 million in 2018. When extrapolated to all employers who self-insure health coverage, potential savings at full biosimilar substitution could have amounted to \$407 million to up to \$1.4 billion in 2018.

Rebates play a major role in biologic and biosimilar reimbursement, and the lack of information on company-specific rebates that might be paid to the pharmacy benefit manager/health plan and the self-insured company may have influenced our savings calculations. Confidential rebates are not available to the general public, but they should be made available to the plan sponsor.

For the biosimilars market to promote price competition and successfully generate savings, it is important that plan sponsors reconsider their options based on the full savings potential offered by each product. Increased transparency and greater access to information are an important first step.

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Exhibit 1. Comparison between the regulatory requirements for approval of biosimilars and generic drugs in the United States

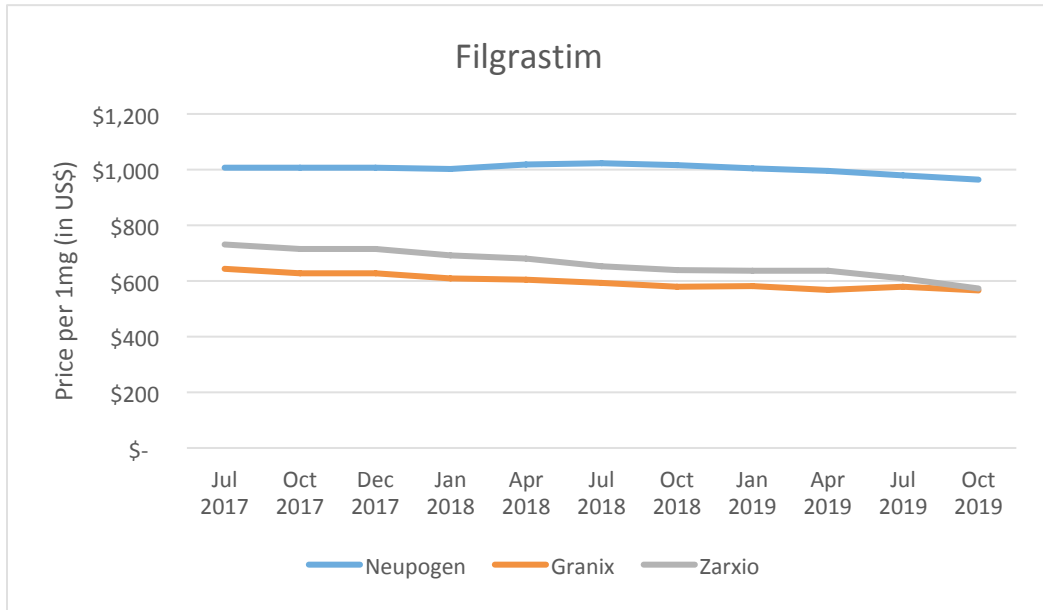
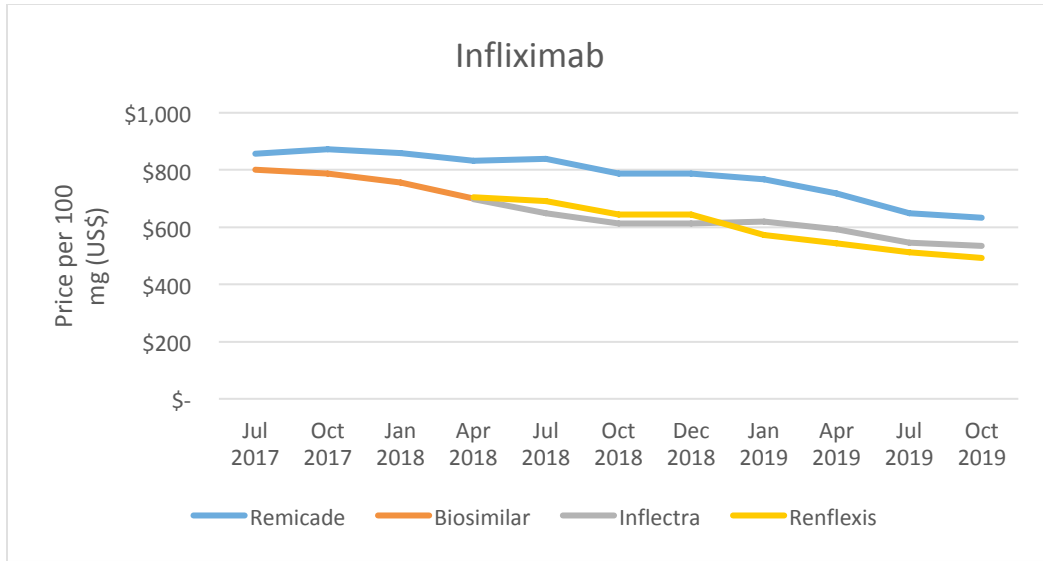
Drug	Biosimilars	Generic Drugs (“Small Molecule”)
Approval Pathway Regulation	Biologics Price Competition and Innovation Act (2010)	Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) (1984)
Approval Requirements¹	<ul style="list-style-type: none"> • Analytical (in-vitro) studies: demonstrate “highly similar” chemical composition to the reference product, purity & quality • Toxicity studies on animal model • Comparative clinical study on patients with the clinical condition: demonstrate safety & effectiveness, assess immunogenicity, pharmacokinetics & pharmacodynamics 	<ul style="list-style-type: none"> • Bioequivalence studies: demonstrate same chemical composition, purity and quality as the reference product, & same bioavailability in healthy volunteers
Criteria for allowing for the drug to be substitutable for the reference product by the pharmacist without the intervention of the prescriber²	<ul style="list-style-type: none"> • Fulfillment of all criteria for biosimilarity; plus: • Clinical “switching” studies: demonstrate same clinical result in any given patient; demonstrate that risk from switching is not greater than using reference product alone 	<ul style="list-style-type: none"> • Automatically granted upon fulfillment of bioequivalence criteria described above
Non-proprietary naming of product³	United States Adopted Names Council (USAN)-designated proper name of the biologic <i>plus</i> a four-letter suffix devoid of meaning	Same USAN-designated proper name as the reference drug

Notes: ¹. The specific studies required for biosimilar approval may vary on a case-by-case basis; ². This property is called “interchangeability” in the case of biosimilars. As of March 2020, these rules will not apply to biosimilar insulins. ³. The non-proprietary names of all reference biologics approved by the FDA on or after March, 2020 will *also* contain a four-letter suffix devoid of meaning, which will be different than the suffix of their biosimilars. Exhibit adapted from Socal, Garrett, Tayler, Bai & Anderson “Naming Convention, Interchangeability, And Patient Interest in Biosimilars” - article forthcoming on *Diabetes Spectrum*, 2020. Source: Food and Drug Administration. <https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-nda>; <https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products#biosimilar>.

Exhibit 2. Overview of FDA-Approved Biosimilars as of December, 2019

Brand Name	Non-Proprietary Name	Product Type	FDA Approval Date	US Market Launch Date
<u>Neupogen</u>	<u>Filgrastim</u>	<u>Reference</u>	<u>1991</u>	<u>1991</u>
Zarxio	filgrastim-sndz	biosimilar	2015	2015
Nivestym	filgrastim-aafi	biosimilar	2018	2018
<u>Remicade</u>	<u>Infliximab</u>	<u>Reference</u>	<u>1998</u>	<u>1998</u>
Inflectra	infliximab-dyyb	biosimilar	2016	2016
Renflexis	infliximab-abda	biosimilar	2017	2017
Ixifi	infliximab-qbtx	biosimilar	2017	n/a
<u>Neulasta</u>	<u>Pegfilgrastim</u>	<u>Reference</u>	<u>2002</u>	<u>2003</u>
Fulphila	pegfilgrastim-jmdb	biosimilar	2018	2018
Udenyca	pegfilgrastim-cbqv	biosimilar	2018	2019
<u>Epogen, Procrit</u>	<u>Epoetin alfa</u>	<u>Reference</u>	<u>1989</u>	<u>1989</u>
Retacrit	epoetin alfa-epbx	biosimilar	2018	2018
<u>Rituxan</u>	<u>Rituximab</u>	<u>Reference</u>	<u>1997</u>	<u>1997</u>
Truxima	rituximab-abbs	biosimilar	2018	2019
<u>Avastin</u>	<u>Bevacizumab</u>	<u>Reference</u>	<u>2004</u>	<u>2004</u>
Mvasi	bevacizumab-awwb	biosimilar	2017	2019
Zirabev	bevacizumab-bvzr	biosimilar	2019	2019
<u>Herceptin</u>	<u>Trastuzumab</u>	<u>Reference</u>	<u>1998</u>	<u>1998</u>
Ogivri	trastuzumab-dkst	biosimilar	2017	2019
Kanjinti	trastuzumab-anns	biosimilar	2019	2019
Ontruzant	trastuzumab-dttb	biosimilar	2019	n/a
Herzuma	trastuzumab-pkrb	biosimilar	2018	n/a
Trazimera	trastuzumab-qyyp	biosimilar	2019	n/a
<u>Enbrel</u>	<u>Etanercept</u>	<u>Reference</u>	<u>1988</u>	<u>1998</u>
Erelzi	etanercept-szsz	biosimilar	2016	n/a
Eticovo	etanercept-ykro	biosimilar	2019	n/a
<u>Humira</u>	<u>Adalimumab</u>	<u>Reference</u>	<u>2002</u>	<u>2003</u>
Hyrimoz	adalimumab-adaz	biosimilar	2018	Expected 2023
Cyltezo	adalimumab-adbm	biosimilar	2017	Expected 2023
Amjevita	adalimumab-atto	biosimilar	2016	Expected 2023

Exhibit 3. ASP Price Trajectories of Filgrastim and Infliximab Biosimilars and Biologics, 2017-2019



Source: Medicare Part B Drug Average Sales Price. Retrieved from: <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice>. Manufacturer's ASP must be calculated by the manufacturer and submitted to CMS every calendar quarter. ASP is a market-based price that reflects the weighted average of all manufacturer sales prices and includes all rebates and discounts that are privately negotiated between manufacturers and purchasers (with the exception of Medicaid and certain federal discounts and rebates). This methodology mirrors reimbursement for physician-administered drugs in the commercial market. (source: <https://catalyst.phrma.org/medicare-monday-what-is-asp>)

Exhibit 4. Study drugs: Reference Biologics and Corresponding Biosimilars

4a) INFLIXIMAB

Main Uses: Immunosuppressant treatment for patients with auto-immune conditions

Therapeutic Category: ¹ Anti-rheumatic, disease modifying; gastrointestinal agent, miscellaneous; immunosuppressant agent; monoclonal antibody; tumor necrosis factor (TNF) blocking agent

Products	Commercially Available Preparations¹ (Route of Administration, Dosage Form, & Strength)	FDA- Approved Indications²
<p>REMICADE (infliximab)</p> <p>Reference Biologic</p> <p>US market launch: 1998</p>	<p>Intravenous use. Reconstituted solution [preservative-free]: 100mg</p>	<ol style="list-style-type: none"> 1. Crohn’s disease 2. Pediatric Crohn’s disease 3. Ulcerative colitis 4. Pediatric ulcerative colitis 5. Rheumatoid Arthritis (in combination with methotrexate) 6. Ankylosing spondylitis 7. Psoriatic arthritis 8. Plaque psoriasis
<p>INFLECTRA (infliximab-dyyb)</p> <p>Biosimilar</p> <p>US launch: 2016</p>	<p>Intravenous use. Reconstituted solution 100mg</p>	<p>Same as Remicade, all indications</p>
<p>RENFLEXIS (infliximab-adba)</p> <p>Biosimilar</p> <p>US launch: 2017</p>	<p>Intravenous use. Reconstituted solution [preservative-free]: 100mg</p>	<p>Same as Remicade, all indications</p>

Sources: ¹Wolters-Kluwer Lexicomp® online drug database. <https://online.lexi.com/lco/action/home>;

²FDA Online Label Repository <https://labels.fda.gov/>

4b) FILGRASTIM

Main Use: adjunctive treatment for patients undergoing chemotherapy
Therapeutic Category: ¹ Colony Stimulating Factor; Hematopoietic Agent

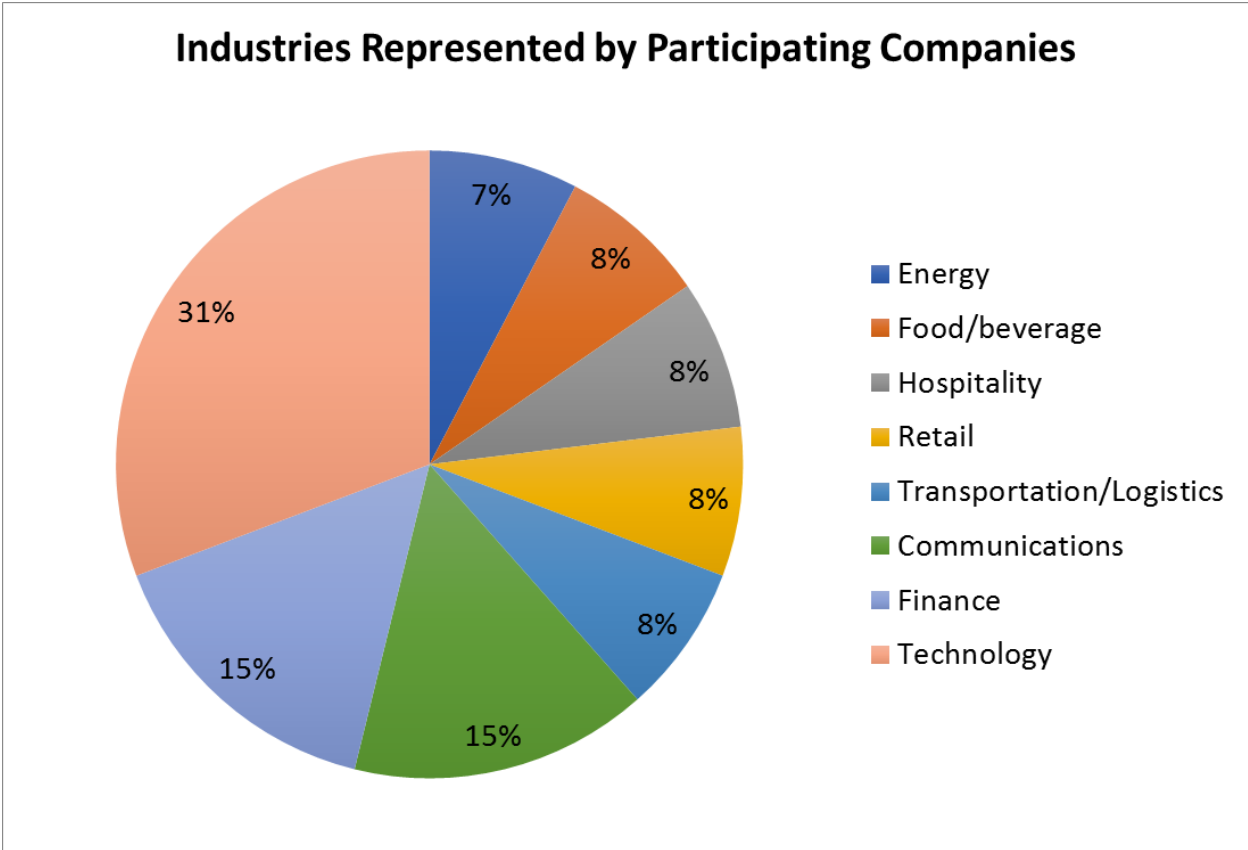
Products	Commercially Available Preparations¹ (Route of Administration, Dosage Form, & Strength)	FDA- Approved Indications²
<p>NEUPOGEN (filgrastim)</p> <p>Reference Biologic</p> <p>US market launch: 1991</p>	<p>Intravenous or subcutaneous</p> <p>Solution: 300 mcg/mL (1 mL); 480 mcg/1.6 mL (1.6 mL)</p> <p>Solution Prefilled Syringe: 300 mcg/0.5 mL (0.5 mL); 480 mcg/0.8 mL (0.8 mL)</p>	<ol style="list-style-type: none"> 1. Patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs with a significant incidence of severe neutropenia with fever 2. Patients with acute myeloid leukemia 3. Patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation 4. Blood for collection by leukapheresis 5. Congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia 6. Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)
<p>ZARXIO (filgrastim-sndz)</p> <p>Biosimilar</p> <p>US launch: 2015</p>	<p>Intravenous or subcutaneous</p> <p>Solution Prefilled Syringe [preservative free]: 300 mcg/0.5 mL (0.5 mL); 480 mcg/0.8 mL (0.8mL)</p>	<p>Same as Neupogen <u>except #6</u></p>
<p>GRANIX (tbo-filgrastim)</p> <p>Alternative Biologic</p> <p>US launch: 2013</p>	<p>Subcutaneous</p> <p>Solution, [preservative free]: 300 mcg/mL (1 mL); 480 mcg/1.6 mL (1.6 mL)</p> <p>Solution Prefilled Syringe, [preservative free]: 300 mcg/0.5 mL (0.5 mL) 480 mcg/0.8 mL (0.8 mL)</p>	<p><u>Only</u> approved for Neupogen’s #1 indication (Patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs with a significant incidence of severe neutropenia with fever)</p>

Sources: ¹Wolters-Kluwer Lexicomp® online drug database. <https://online.lexi.com/lco/action/home>;

²FDA Online Label Repository <https://labels.fda.gov/>

Note: Our study also requested data on the biosimilar Nivestym (launched 2018), but there was no utilization reported by any participating companies in the year 2018.

Exhibit 5. Overview of Industries Represented by the Participating Companies



Source: N=13 ERIC member companies that donated data for this study.

Exhibit 6. Characteristics of Participating Companies

Overall Benefit	Avg (sd)	Min - Max
Number of Users (in thousands)	174.8 (143.7)	21 – 484
Number of Claims/year (in thousands)	2051.9 (1503.7)	154 – 4,469
Drug Spending (in \$ millions)	\$ 273.3 (198.8)	\$ 29 - \$ 569

Notes: The table reflects 11 ERIC member companies with information, and the benefit types for which the companies provided information (medical or prescription). Two companies did not provide full information and are therefore not included in this description.

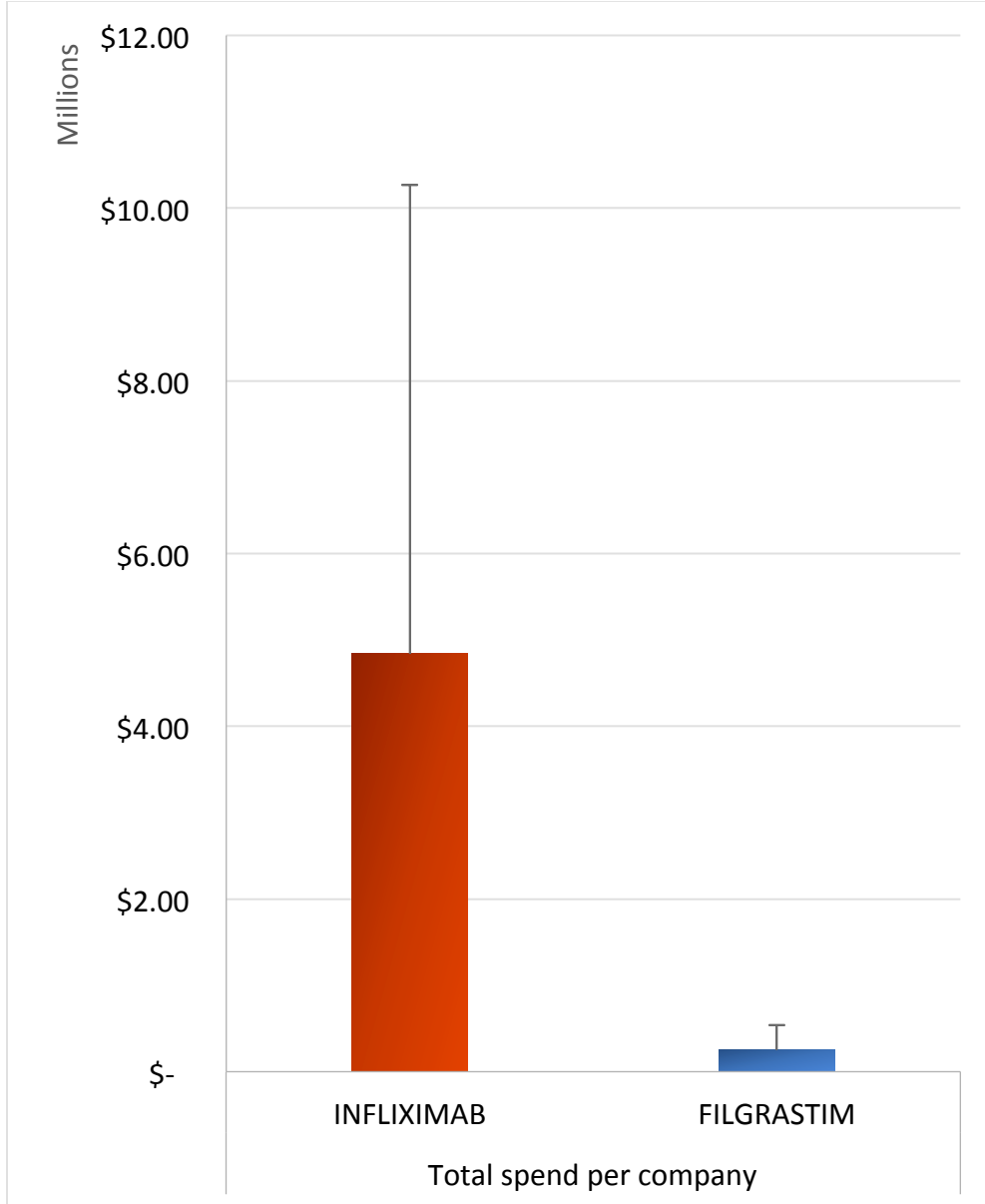
Exhibit 7. Overview of Study Drugs: Utilization and Spending

Drugs of Interest	Avg (sd)	Min - Max
Users¹		
Number of Users	186 (209)	18 - 683
Average Age	48.7 (10.7)	9.7 - 74
% Female	55% (14%)	26% - 81%
Claims¹		
Number of Claims	1,176 (1,146)	72 - 3,507
Spending¹		
Drug Spending (in millions)	\$4.7 (\$5.6)	\$288 thousand - \$16.6 million
% of Company's Overall Benefit²		
% of Company's total number of users	0.06% (0.04%)	0.02% - 0.12%
% of Company's total drug claims	0.03% (0.03%)	0.01% - 0.11%
% of Company's overall drug spending	1% (0.9%)	0.18 - 2.7%
Distribution Channel: Medical vs. Prescription²		
% Claims through medical benefit	83.2% (22%)	37.9% - 99.5%
% Spend through medical benefit	86% (24%)	14.6% - 100%

Notes: ¹ N=13 ERIC member companies. ² N=11 ERIC member companies with information.

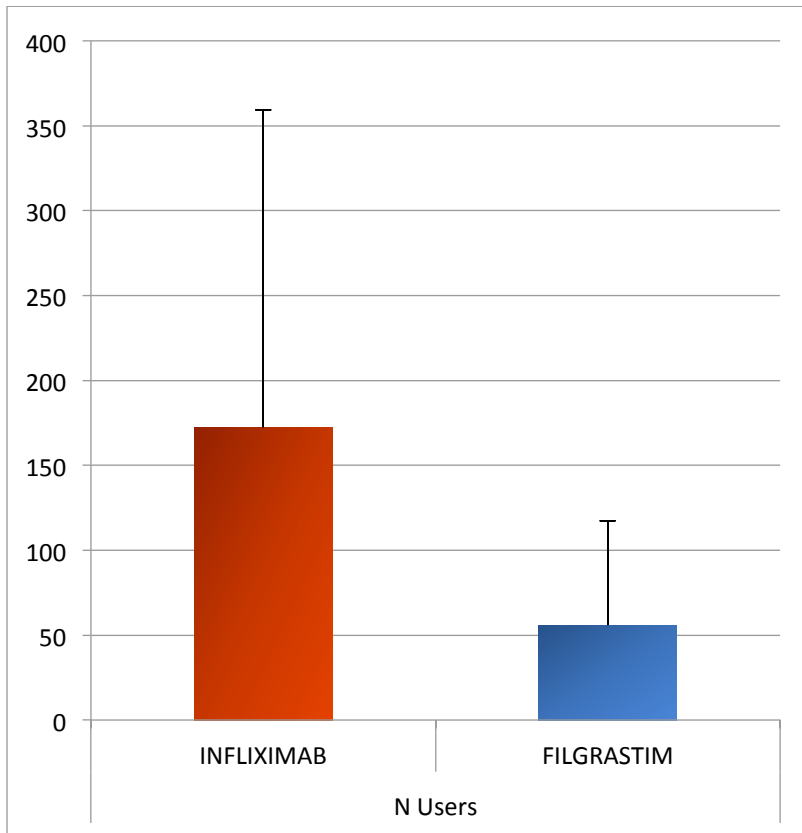
Exhibit 8. A Comparison Between the Two Study Drugs: Infliximab and Filgrastim

8a) Total Spending per Company



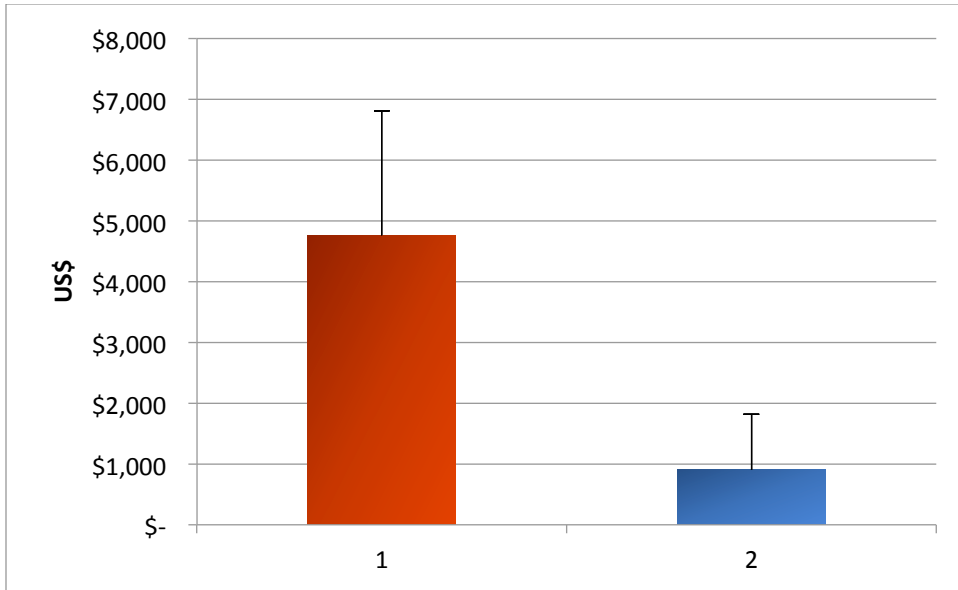
Note: Average and standard deviation for the year 2018. Data aggregated from medical and prescription drug benefit from 13 ERIC member companies.

8b) Number of Users per Company



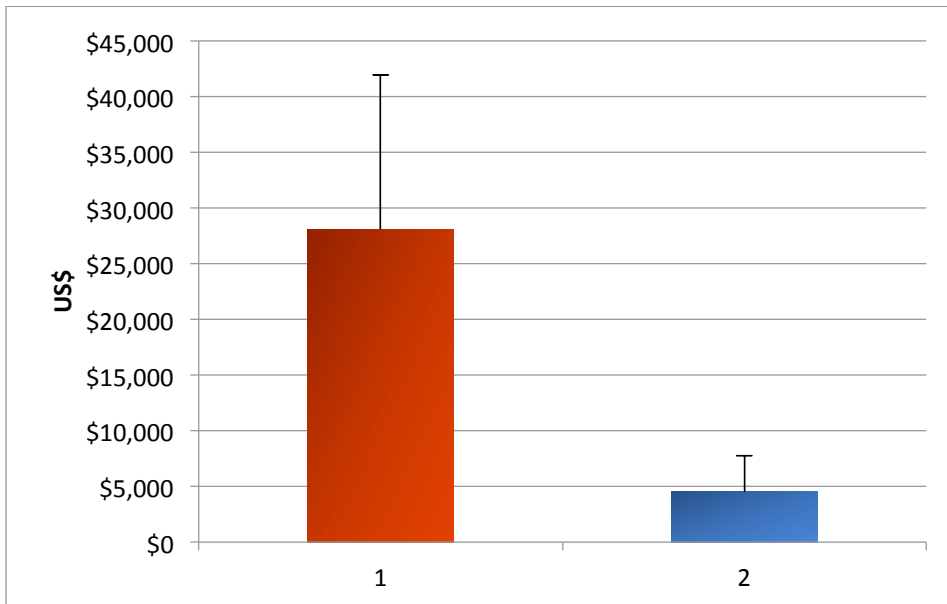
Note: Average and standard deviation for the year 2018. Data aggregated from medical and prescription drug benefit from 13 ERIC member companies.

8c) Plan Sponsor (Company) Spending per Claim



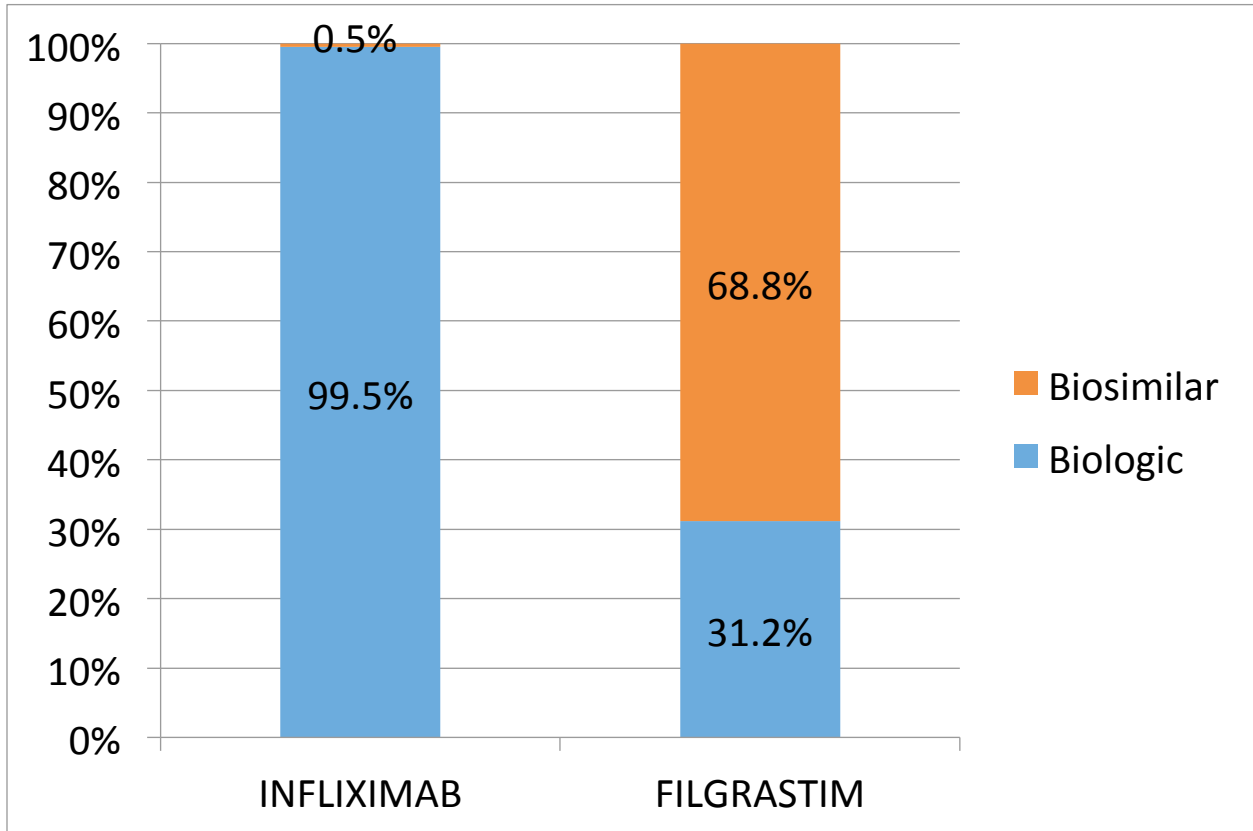
Note: Estimates reflect average and standard deviation, weighted by the number of claims, for the year 2018. Data aggregated from medical and prescription drug benefit from 13 ERIC member companies. Drug 1: Infliximab; Drug 2: filgrastim.

8d) Plan Sponsor (Company) Spending per User



Note: Estimates reflect average and standard deviation, weighted by the number of users, for the year 2018. Data aggregated from medical and prescription drug benefit from 13 ERIC member companies. Drug 1: Infliximab; Drug 2: filgrastim.

Exhibit 9. Overall Biosimilar Market Share: Comparison between the Study Drugs



Note: Estimates reflect average market share, for the biosimilar vs. the biologic, among all claims for the drug during the year 2018. Data from N=26 (infliximab) and N=28 (filgrastim) medical and prescription drug benefit carriers (“data donors”) representing 13 ERIC member companies.

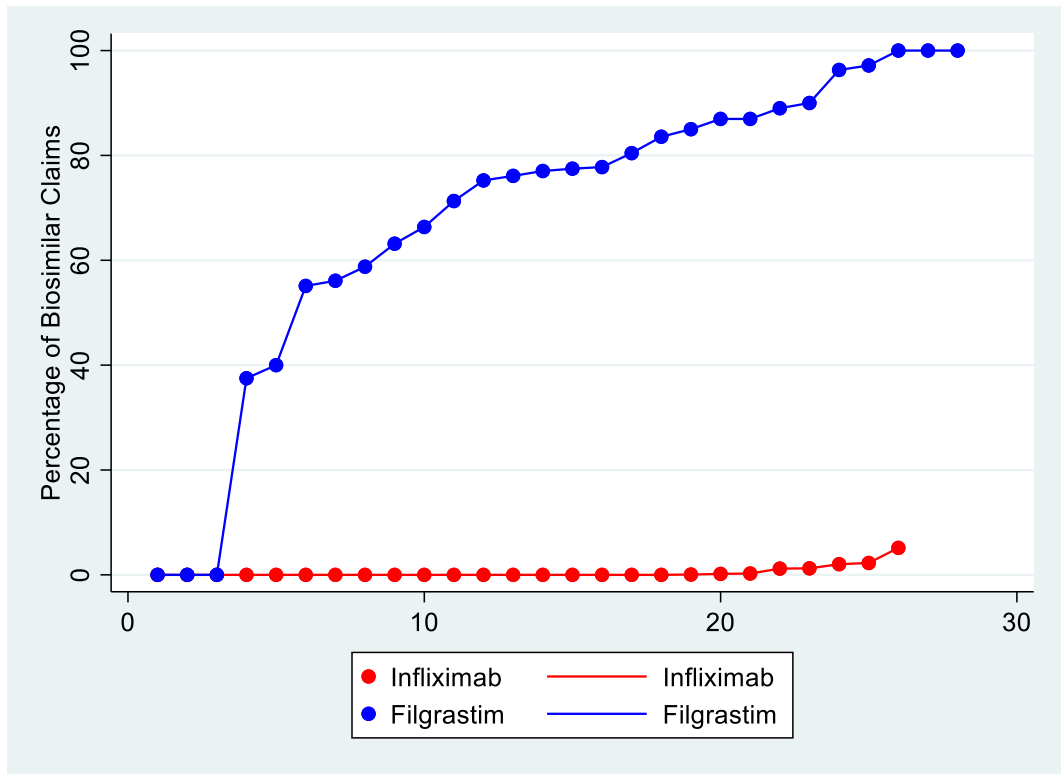
Exhibit 10. Biosimilar Market Share per Study Drug & Data Donor

10a) Overview

Percentage of Biosimilar Claims	Avg (sd)	Minimum %	Maximum %
INFLIXIMAB	0.54% (1.14%)	0%	5.14%
FILGRASTIM	68.8% (29.4%)	0%	100%

N=26 data donors for infliximab, 28 data donors for filgrastim

10b) Comparison by Drug and Data Donor



N=26 data donors for infliximab, 28 data donors for filgrastim

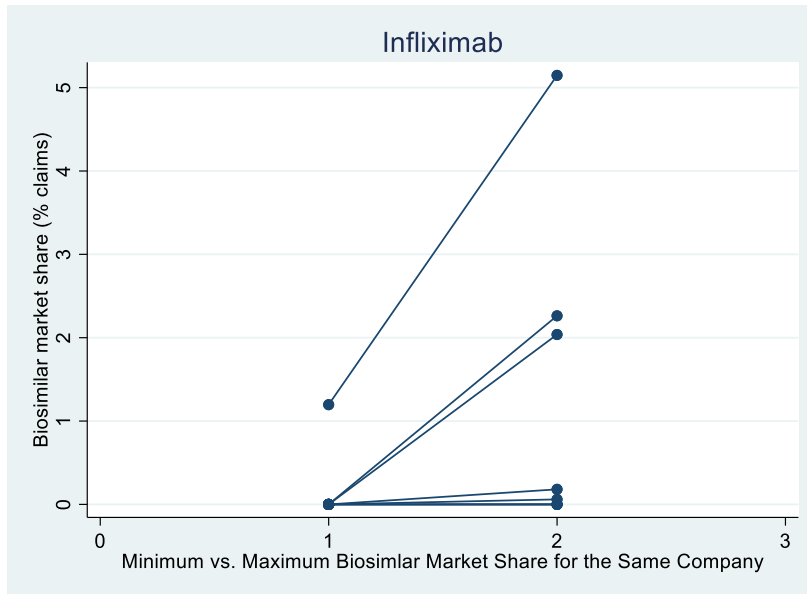
Exhibit 11. Variation in Biosimilar Market Share within Each Participating Company

11a) Overview (companies with 2+ donors)

Difference within company	Avg (sd)	Minimum %	Maximum %
INFLIXIMAB	1% (1.3%)	0%	4%
FILGRASTIM	41% (31%)	6.1%	100%

N=11 companies with two or more data donors

11b) INFLIXIMAB



11c) FILGRASTIM

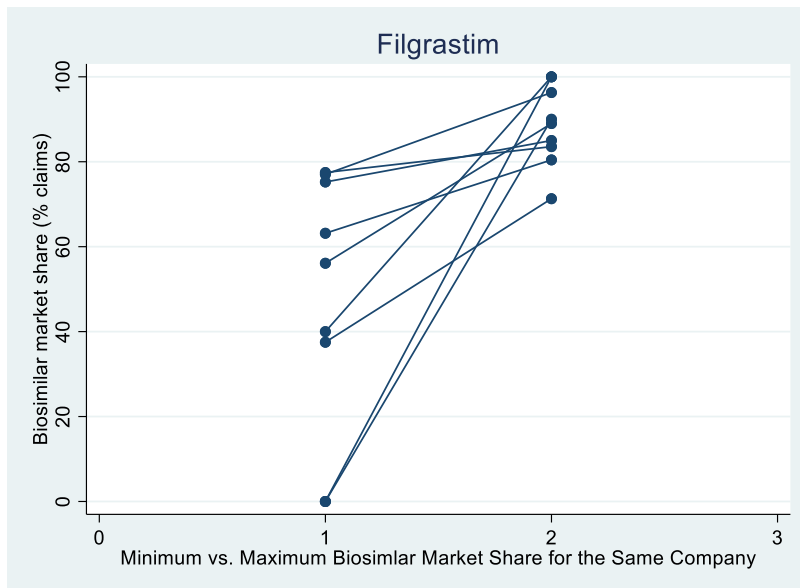


Exhibit 12. Characterization of Patients Using Reference Biologic and Biosimilar Products

12a) INFLIXIMAB

	Biologic	Biosimilar	p-value
Average Age (95% CI)¹	40.6 (40.6 – 40.7)	46.5 (46 – 47.9)	<0.001
% Female (95% CI)¹	45.7% (45.5%-45.8%)	71.4% (69.2% - 73.6%)	<0.001
% Off-label use (95% CI)²	11.3% (10.7% - 11.9%)	9.7% (8.0% - 11.4%)	NS

Notes: ¹N = 12,621 claims with information; estimates obtained by linear regression weighted by the number of claims for each drug. ²N=1,106 beneficiaries with information; estimates obtained by independent samples t-tests with equal variances. NS: p-value > 0.05.

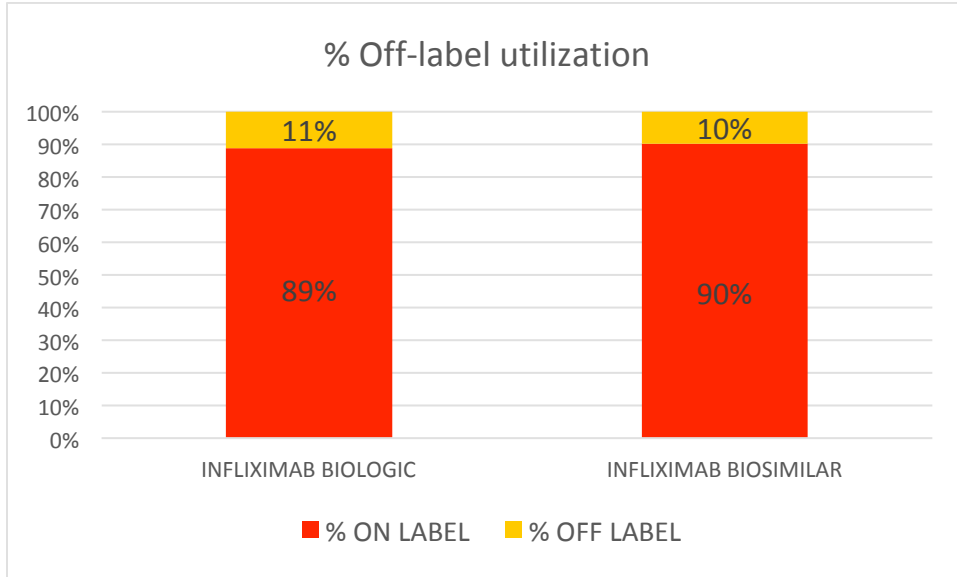
12b) FILGRASTIM

	Biologic	Biosimilar	p-value
Average Age (95% CI)¹	50.4 (50.1-50.8)	53.3 (53.0-53.5)	<0.0001
% Female (95% CI)¹	61.8% (60.6% - 62.8%)	60% (59.2% - 60.8%)	0.014
% Off-label use (95% CI)²	8.8% (7.2% - 10.4%)	9.5% (8.0% - 11.0%)	NS

Notes: ¹N = 3,455 claims with information; estimates obtained by linear regression weighted by the number of claims for each drug. ²N=228 beneficiaries with information; estimates obtained by independent samples t-tests with equal variances. NS: p-value > 0.05.

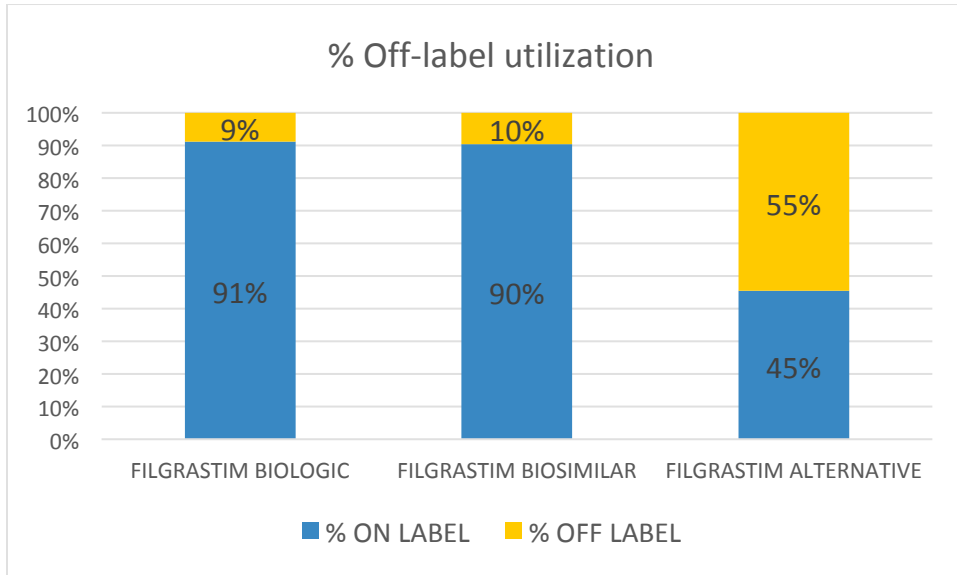
Exhibit 13. Clinical Conditions for which Study Drugs Were Prescribed: Biologics vs. Biosimilars

13a) INFLIXIMAB



Notes: N= 10 ERIC member companies with information.

13b) FILGRASTIM



Notes: N= 10 ERIC member companies with information.

Exhibit 14. How are patients paying for their drug? A Comparison between biologic and biosimilars

14a) INFLIXIMAB

INFLIXIMAB	Biologic	Biosimilar	p-value
% Requires Coinsurance (95% CI) ^{1,a}	85.4% (84.6%-86.2%)	76.7% (64%-89.3%)	NS
Average Coinsurance Level (95% CI) ^{1,b}	20.5% (20.4%-20.6%)	20% (17.8%-20.7%)	NS
Average Out-of-Pocket Spending (95% CI) ^{2,c}	\$ 2,890.27 (2,851.55 - 2,929.00)	\$ 2,553.20 (2,207.72 – 2,898.68)	0.056
Difference between biosimilar and biologic out-of-pocket costs ^{2,c} Average (%)		\$ -337.07 (12%)	

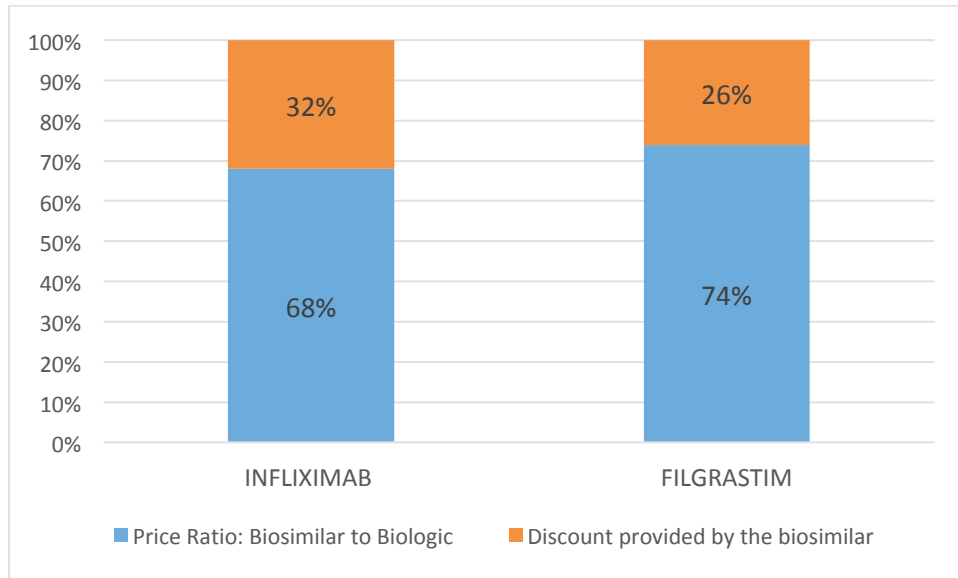
Notes: ¹N = 4,117 claims with information. ²N= 6,446 claims with information. ^aFrequency in which members are required to pay a coinsurance (i.e., a percentage of the drug’s cost) in order to obtain the drug they need, as opposed to a paying a fixed-dollar copay. ^bAverage percentage of the drug cost that patients are required to pay, among those for whom coinsurance is required. ^cAverage cost paid by the patient for the drug over the course of the year, regardless of their type of cost-share (copay or coinsurance). Estimates obtained by linear regression weighted by the number of claims for each drug. CI: confidence interval. NS: not statistically significant (p-value greater than 0.05).

14b) FILGRASTIM

FILGRASTIM	Biologic	Biosimilar	p-value
% Requires Coinsurance (95% CI) ^{1,a}	95.2% (92.7%-97.7%)	90.8% (89.4%-92.2%)	0.003
Average Coinsurance Level (95% CI) ^{1,b}	22.4% (21.6%-23.2%)	22.1% (21.7%-22.5%)	NS
Average Out-of-Pocket Spending (95% CI) ^{2,c}	\$ 1,319.87 (1,244.17 – 1,395.57)	\$ 721.01 (675.07 - 766.96)	<0.0001
Difference between biosimilar and biologic out-of-pocket costs ^{2,c} Average (%)		\$ -598.86 (45%)	

Notes: ¹N = 1,338 claims with information. ²N=2,827 claims with information ^aFrequency in which members are required to pay a coinsurance (i.e., a percentage of the drug’s cost) in order to obtain the drug they need, as opposed to a paying a fixed-dollar copay. ^bAverage percentage of the drug cost that patients are required to pay, among those for whom coinsurance is required. ^cAverage cost paid by the patient for the drug over the course of the year, regardless of their type of cost-share (copay or coinsurance). Estimates obtained by linear regression weighted by the number of claims for each drug. CI: confidence interval. NS: not statistically significant (p-value greater than 0.05).

Exhibit 15. How are Plan Sponsors paying for the drugs? Price differential between the biosimilar and reference biologic



Note: data reflects median ratios of the price of the biosimilar to the biologic, and corresponding discounts offered by the biosimilar over the price of the biologic, for the two drugs under study. In the case of infliximab, biologic prices reflect average cost per claim of Remicade® and biosimilar prices reflect average cost per claim of Inflectra®. In the case of filgrastim, biologic prices reflect average cost per claim of Neupogen® and biosimilar prices reflect average cost per claim of Zarxio®. Price comparisons are based on the analysis of drug claims in the study sample, matching biosimilar and reference biologic by the same active ingredient, dosage form and strength, within the same plan sponsor (ERIC member company) and data donor (medical or prescription benefit vendor). Price comparisons included only drugs where claims for the biologic and biosimilar contained a similar number of units and where the vendor had reimbursed at least one claim for the reference biologic and all corresponding biosimilars over the course of the year. N=2 comparison groups for infliximab; 7 comparison groups for filgrastim.

Exhibit 16. How much could companies save under increased biosimilar utilization? An Overview

16a) INFLIXIMAB

Savings	Average (sd)	Min	Max
100% biosimilar substitution (in US\$ million)	\$ 1.53 (\$ 1.72)	\$ 723 thousand	\$ 4.93
50% biosimilar substitution	\$ 739,987 (\$ 828,149)	\$ 32,787	\$ 2.32 million

Note: data reflects estimated savings at different levels of biosimilar substitution, utilizing the ratio between biosimilar and biologic prices identified in the matched analysis of drug claims from the study sample. N=13 participating ERIC member companies, totaling 26 different data donors.

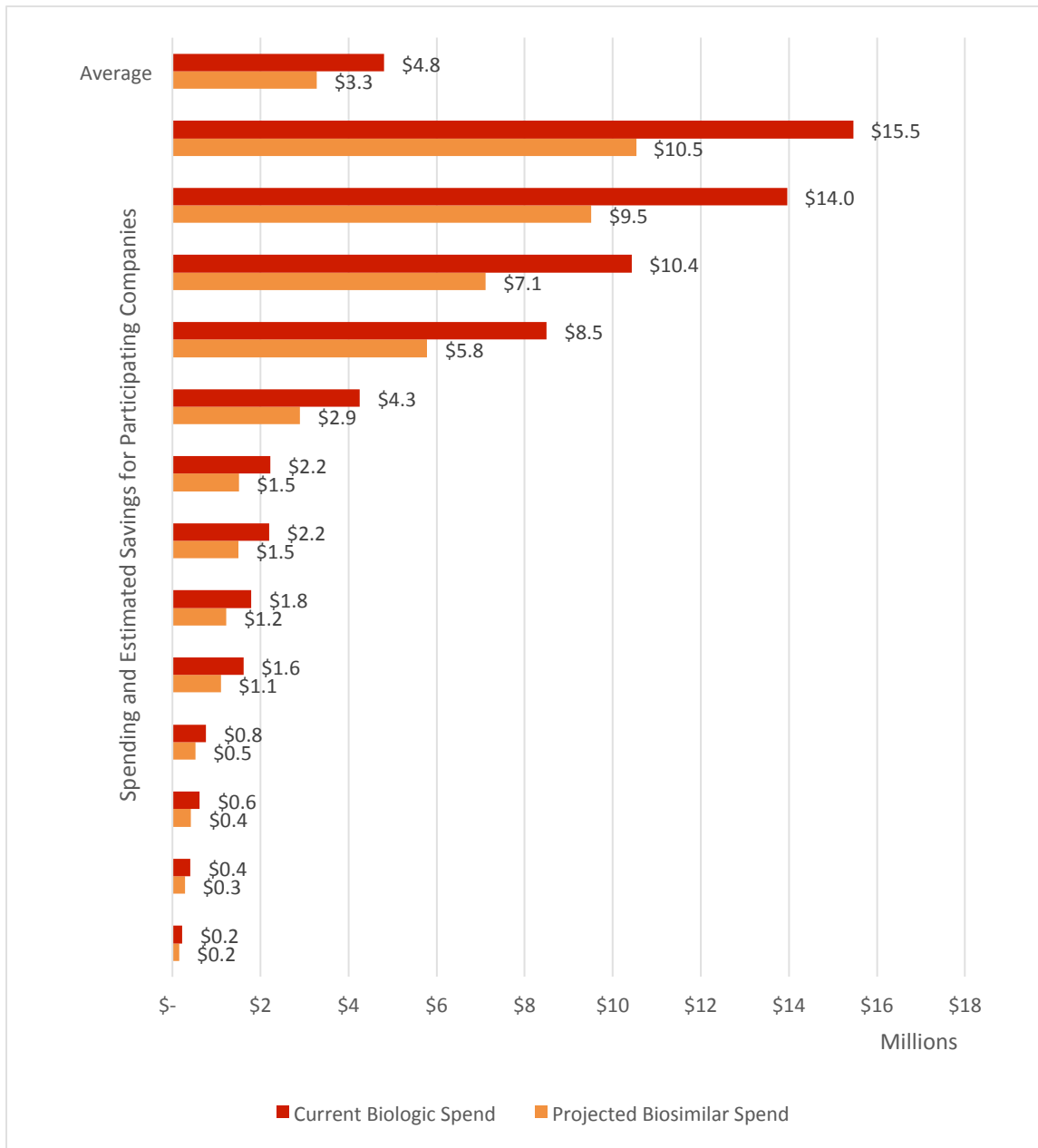
16b) FILGRASTIM

Savings (in US\$)	Average (sd)	Min	Max
100% biosimilar substitution	\$ 17,838.01 (\$ 24,112.91)	\$2,281.76	\$87,801.74

Note: data reflects estimated savings at full biosimilar substitution, utilizing the ratio between biosimilar and biologic prices identified in the matched analysis of drug claims from the study sample. The analysis of 50% biosimilar substitution was not performed because most companies are already over 50% biosimilar filgrastim utilization. N=13 participating ERIC member companies, totaling 28 different data donors.

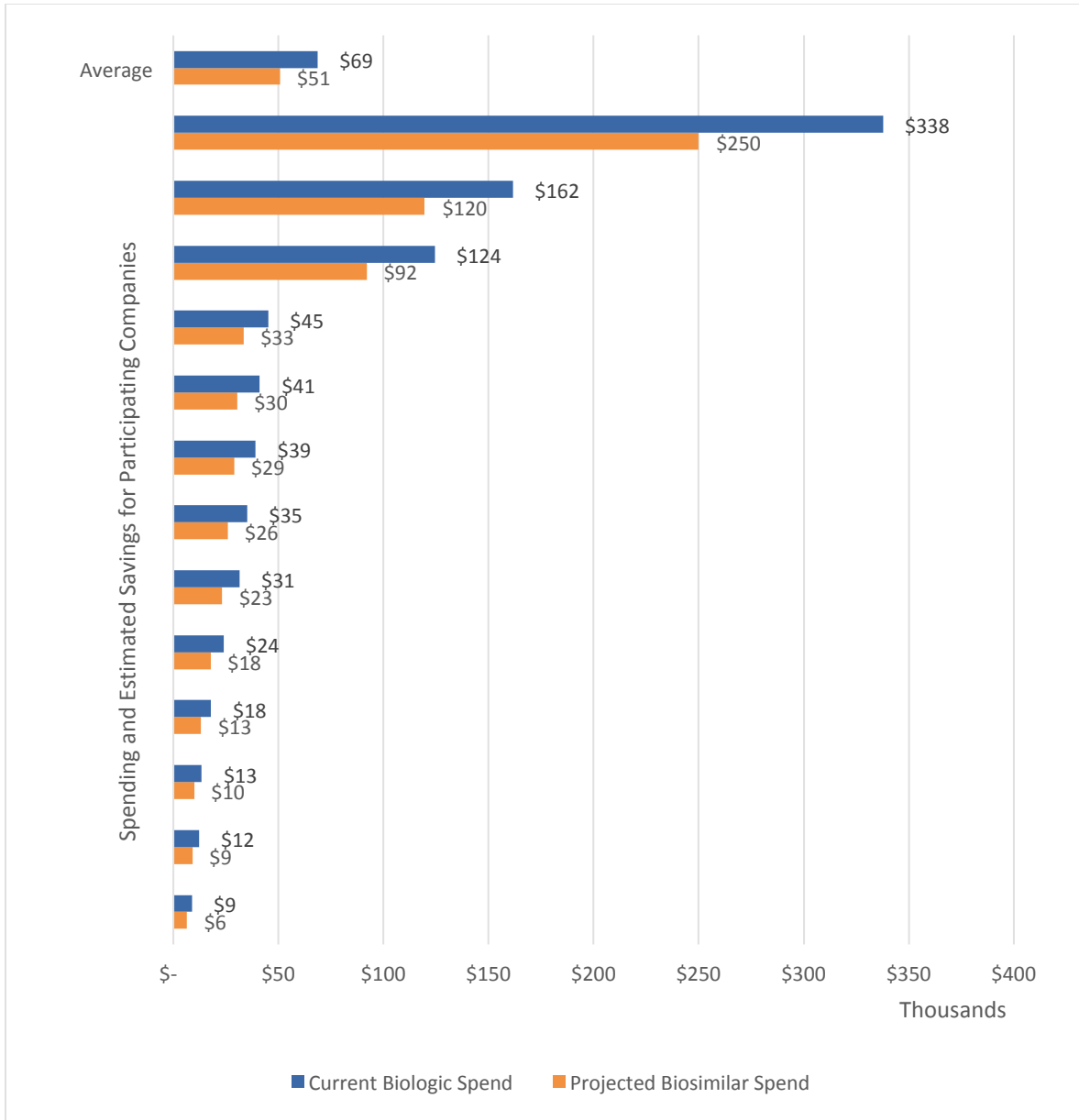
Exhibit 17. Estimated Savings per Plan Sponsor: A Comparison with Current Spending Levels

17a) INFLIXIMAB



Source: Data reflects N=13 participating ERIC member companies, totaling 26 different data donors (prescription drug and medical benefit vendors).

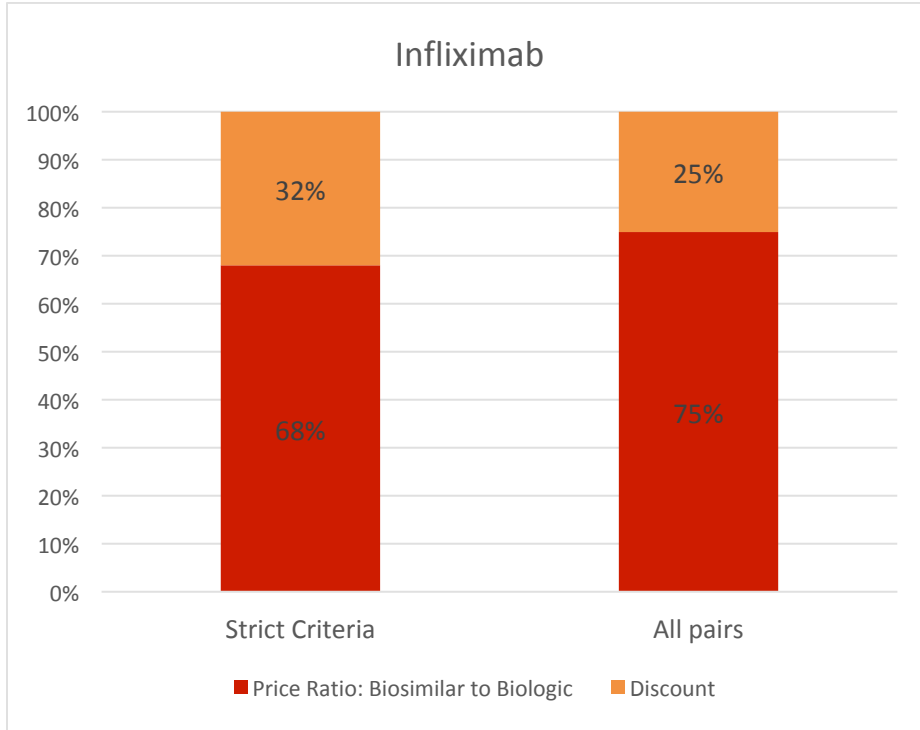
17b) FILGRASTIM



Source: Data reflects N=13 participating ERIC member companies, totaling 28 different data donors (prescription drug and medical benefit vendors).

Exhibit 18. Sensitivity Analysis (Part 1): A comparison of price differentials in this study

18a) INFLIXIMAB

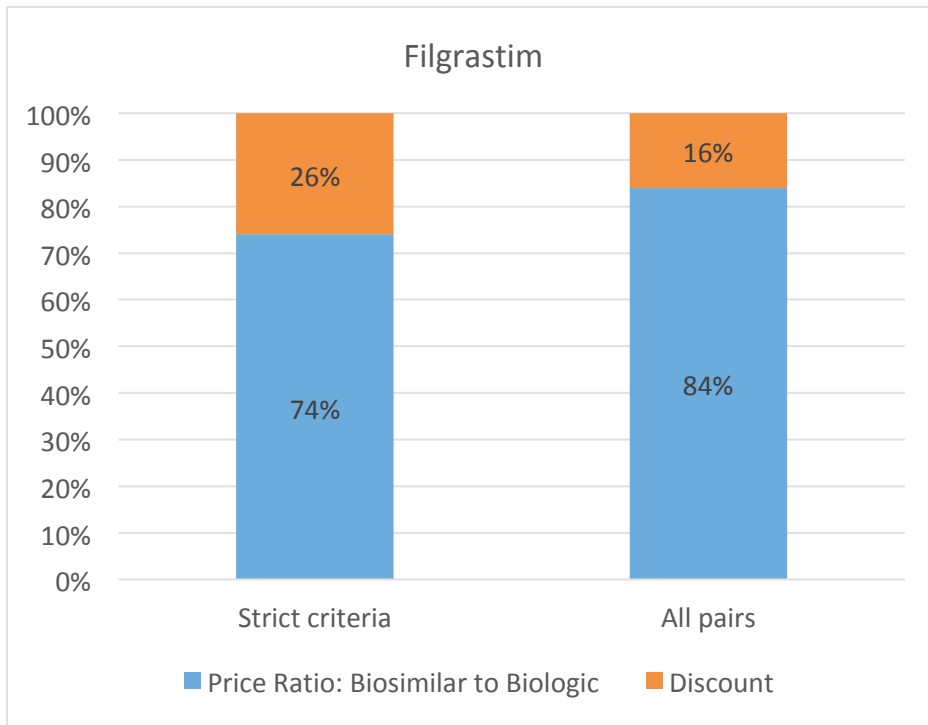


Note: data reflects median ratios of the price of the biosimilar to the biologic, and corresponding discounts offered by the biosimilar over the price of the biologic, for the drugs under study. Infliximab prices reflect average cost per claim of reference biologic Remicade® and biosimilar Inflectra®.

“Strict criteria” reflect price comparisons obtained by matching biosimilar and reference biologic by the same active ingredient, dosage form and strength, within the same plan sponsor (ERIC member company) and data donor (medical or prescription benefit vendor). Price comparisons included only drugs where claims for the biologic and biosimilar contained a similar number of units and where the vendor had reimbursed at least one claim for the reference biologic and all corresponding biosimilars over the course of the year. N=2 comparison groups.

“All pairs” reflect price comparisons obtained by matching biosimilar and reference biologic by the same active ingredient, dosage form and strength, within the same plan sponsor (ERIC member company) and data donor (medical or prescription benefit vendor). N=8 comparison groups.

18b) FILGRASTIM



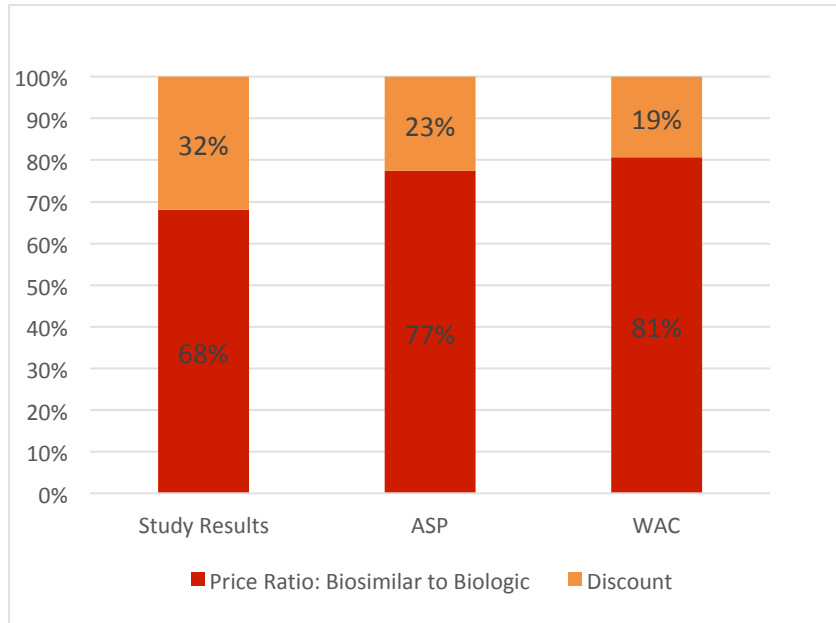
Note: data reflects median ratios of the price of the biosimilar to the biologic, and corresponding discounts offered by the biosimilar over the price of the biologic, for the drugs under study. Filgrastim prices reflect average cost per claim of reference biologic Neupogen® and biosimilar Zarxio®.

“Strict criteria” reflect price comparisons obtained by matching biosimilar and reference biologic by the same active ingredient, dosage form and strength, within the same plan sponsor (ERIC member company) and data donor (medical or prescription benefit vendor). Price comparisons included only drugs where claims for the biologic and biosimilar contained a similar number of units and where the vendor had reimbursed at least one claim for the reference biologic and all corresponding biosimilars over the course of the year. N=7 comparison groups.

“All pairs” reflect price comparisons obtained by matching biosimilar and reference biologic by the same active ingredient, dosage form and strength, within the same plan sponsor (ERIC member company) and data donor (medical or prescription benefit vendor). N=29 comparison groups.

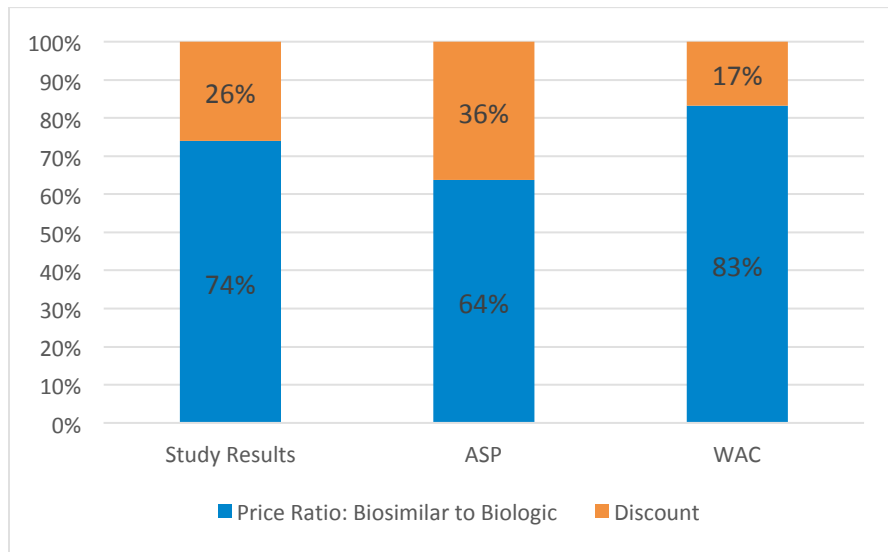
Exhibit 19. Sensitivity Analysis (Part 2): A comparison with external price benchmarks

19A) INFLIXIMAB



Source: Study estimates reflect median discount across company claims matched by strict criteria. ASP: average sales price obtained from July 2018 CMS Payment limit. Price differential adjusted for 6% provider fee. WAC: wholesale acquisition cost. Differentials presented for infliximab 100mg/10ml Remicade® and Inflectra®.

19B) FILGRASTIM



Source: Study estimates reflect median discount across company claims matched by strict criteria. ASP: average sales price obtained from July 2018 CMS Payment limit. Price differential adjusted for 6% provider fee. WAC: wholesale acquisition cost. Differentials presented for filgrastim 300mcg/0.5mL Neupogen® and Zarxio®.